FINAL REPORT

Pre-Demonstration Development of Controlled-Release Corrosion Inhibitors and Healing Agents as Alternatives to Hexavalent Chromium

SERDP Project WP18-E1-1531

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May 31, 2019

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	**2. REPORT TYPE**	**3. DATES COVERED** *(From - To)*
31-05-2019	SERDP Final Report	March 2018-May 2019

4. TITLE AND SUBTITLE
Pre-Demonstration Development of Controlled-Release Corrosion Inhibitors and Healing Agents as Alternatives to Hexavalent Chromium

5a. CONTRACT NUMBER

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER
WP18-E1-1531

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
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8. PERFORMING ORGANIZATION REPORT NUMBER
WP18-E1-1531

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Strategic Environmental Research and Development Program
4800 Mark Center Drive, Suite 17D03
Alexandria, VA 22350-3605

10. SPONSOR/MONITOR'S ACRONYM(S)
SERDP

11. SPONSOR/MONITOR'S REPORT NUMBER(S)
WP18-E1-1531

12. DISTRIBUTION / AVAILABILITY STATEMENT
Distribution A: Unlimited public release

13. SUPPLEMENTARY NOTES
None Available

14. ABSTRACT This Limited Scope Study was directed to achieve the following objectives:
(1) Scale-up of materials that can meet MIL-PRF-23377 (solvent-based primer).
(2) Provide evidence of resistance to aircraft alkaline cleaners and deicing fluids.
(3) Provide formulation for initial ecological and toxicity screening.
(4) Submit an interim report that will provide the basis for a future ESTCP demonstration effort.
The encapsulation procedure for two corrosion inhibitors was scaled up from lab scale to 2.0 kg. This scale will accommodate high volume production of coatings with encapsulated corrosion inhibitors for large surface areas during a follow on ESTCP demonstration effort. Test results provided evidence of resistance to alkaline cleaners and aircraft deicing fluids and compliance with MIL-PRF-23377. All the MIL-PRF-23377 requirements were met with the exception of the adhesion requirement, in top coated panels, and the flexibility requirement. Work on solving these two problems will be done prior to validation and demonstration of the technology. An initial ecological and toxicity screening identified several factors that were not critical to the acceptance of the encapsulated corrosion inhibitor. This new technology will lead to environmentally friendly alternatives to hexavalent chromium that will enable DoD to protect its assets. Field demonstration, licensing, qualification, and commercialization will allow its real world utilization.

15. SUBJECT TERMS
Alternatives to Hexavalent Chromium, Controlled Release, Corrosion Inhibitors, Self-healing, Corrosion Protection, MIL-PRF-23377, 2-MBT, 8-HQ.

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			Dr. Luz Marina Calle
UU	UU	UU	UU	127	**19b. TELEPHONE NUMBER** *(include area code)* 321-867-3278

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LIST OF ACRONYMS

2-MBT	2-mercaptobenzothiazole
8-HQ	8-Hydroxyquinoline
AFRL	Air Force Research Laboratory
AMI	Autonomic Materials Inc.
APCH	Army Public Health Center
ASTM	American Society for Testing and Materials
Cr(VI)	Hexavalent chromium
DFARS	Defense Federal Acquisition Regulation Supplement
DFT	Dry Film Thickness
DI	Deionized Water
DoD	U.S. Department of Defense
DMF	Dimethylformamide
EMA	Ethylene maleic anhydride
EPA	Environmental Protection Agency
ESTCP	Environmental Security Technology Certification Program
HCl	Hydrochloric Acid
HVLP	High volume/low pressure
MEK	Methyl ethyl ketone
MF	Melamine Formaldehyde
MFPTT	Melamine Formaldehyde Pentaerythritol Tetra (3-Mercapto propionate)
N/A	Not Applicable
NASA	The National Aeronautics and Space Administration
NMP	N-Methylpyrrolidone
OSHA	Occupational Safety and Health Administration
SDS	Sodium dodecyl sulfate
PTT	Pentaerythrytol tetrakis(3-mercaptopropionate)
PVA	Polyvinyl alcohol
SERDP	Strategic Environmental Research and Development Program
SON	Statement of Need
TRL	Technology Readiness Level
USAF	United States Air Force

KEYWORDS

Alternatives to Hexavalent Chromium, Controlled Release, Corrosion Inhibitors, Self-healing, Corrosion Protection, MIL-PRF-23377, 2-MBT, 8-HQ.

ACKNOWLEDGEMENTS

The financial and programmatic support of this Strategic Environmental Research and Development Program (SERDP) project under the direction of Dr. Robin Nissan, Program Manager, and Mr. Braxton V. Lewis, SERDP and ESTCP, Weapons Systems and Platforms Program Area Technical Assistant, is gratefully acknowledged.

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ABSTRACT

Introduction and Objectives: The objective of this "FY18 Strategic Environmental Research and Development Program (SERDP) Limited Scope Pre-Demonstration Development" project was to achieve pre-demonstration development of controlled-release corrosion inhibitors as alternatives to hexavalent chromium [Cr(VI)] (chromate)-containing primers. The proposed Limited Scope Study was directed to achieve the following objectives:(1) Scale-up of materials that can meet MIL-PRF-23377 (solvent-based primer).
(2) Provide evidence of resistance to aircraft alkaline cleaners and deicing fluids.
(3) Provide formulation for initial ecological and toxicity screening.
(4) Submit an interim report that will provide the basis for a future ESTCP demonstration effort.

Technical Approach: AMI achieved the scalability of the encapsulation process for two corrosion inhibitors by starting with a thorough assessment of the laboratory scale process, designed to optimize parameters including surfactant type, surfactant concentration, process temperature profile, process duration, and micro particle yield per batch. Evidence of resistance to alkaline cleaners and aircraft deicing fluids and compliance with MIL-PRF-23377 was gathered by replacing the inhibitor package, of a primer that meets the MIL-PRF-23377 requirements, with an encapsulated inhibitor and self-healing microcapsules. The properties of the primer formulation, that were expected to change, were tested to demonstrate that the primer still met the MIL-PRF-23377 requirements.

Results: The scale-up of the inhibitor encapsulation process for two corrosion inhibitors to the 2.0 kg scale was achieved successfully; evaluation of primer formulations, that incorporated the encapsulated corrosion inhibitors and self-healing agents, provided evidence that the primer formulations met most of the MIL-PRF-23377 requirements and showed sufficient resistance to alkaline cleaners and aircraft deicing fluids; an initial ecological and toxicity screening, on the encapsulated inhibitor formulation, by the Army Public Health Center (APHC) concluded that most of the proposed components are of low to moderate toxicity and are not a significant concern.

Benefits: This new technology will lead to environmentally friendly alternatives to hexavalent chromium that will enable DoD to protect its assets. The scalability of the technology was achieved to a scale that will accommodate a follow on field demonstration effort. The encapsulation technology is currently being evaluated by several industry partners for licensing. Licensing, qualification, and commercialization will allow its real world utilization.

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1. OBJECTIVE

The objective of this Limited Scope study, under SON "FY18 Strategic Environmental Research and Development Program (SERDP) Limited Scope Pre-Demonstration Development" project, was to achieve pre-demonstration development of controlled-release corrosion inhibitors as alternatives to hexavalent chromium [Cr(VI)] (chromate)-containing primers, that are currently used on a variety of weapon systems, prior to the field demonstration and validation effort that was proposed to the FY18 Environmental Security Technology Certification Program (ESTCP) Topic B6: Demonstration/Validation of Alternatives to Hexavalent Chromium in Manufacturing and Maintenance of Weapons Systems Solicitation (Proposal Number WP18-B6-5249 titled Controlled-Release Corrosion Inhibitors and Healing Agents as Alternatives to Hexavalent Chromium). This proposed Limited Scope study was given the specific direction from the Weapons Systems and Platforms Technical Committee to achieve the following objectives:

(1) Scale-up of materials that can meet MIL-PRF-23377[1] (solvent-based primer).
(2) Provide evidence of resistance to aircraft alkaline cleaners and deicing fluids.
(3) Provide formulation for initial ecological and toxicity screening.
(4) Submit an interim report that will provide the basis for a future ESTCP demonstration effort.

The effort to achieve the above objectives involved:

(1) Focusing on the scale-up of the microencapsulation process of corrosion inhibitors, in collaboration with Autonomic Materials Inc. (AMI), to demonstrate producibility to accommodate a follow on field demonstration effort.
(2) Incorporating encapsulated corrosion inhibitor and healing agent into paint formulations provided by PPG, and testing paint properties and coating performance using MIL-PRF-23377 to evaluate the material compatibilities of these encapsulated inhibitors and healing agents.
(3) Performing testing of resistance to aircraft alkaline cleaners and deicing fluids.
(3) Providing formulation information to the Army Public Health Center (APHC), to conduct an initial ecological and toxicity screening.
(4) Submitting this interim report to provide the basis for a follow-on ESTCP demonstration/validation effort.

The achievement of these objectives increased the technology readiness level (TRL), of this hexavalent chromium alternative technology, and reduced the risk of the follow on field test, as it was described in the FY18 ESTCP proposal for Controlled-Release Corrosion Inhibitors and Healing Agents as Alternatives to Hexavalent Chromium.

2. BACKGROUND

2.1 Problem Statement

Hexavalent chromium [Cr(VI)] compounds have been used in coatings and finishes for over a century, providing excellent corrosion protection to different metal substrates in a wide range of environments for various applications.[2] It has been documented since the 1920s that Cr(VI) is carcinogenic in nature, after multiple studies noted an increase in the incidence of nasal and lung cancer among industrial workers in direct contact with Cr(VI) compounds.[3] As a family of known carcinogens, Cr(VI) compounds have become the most stringently regulated materials used in manufacturing and maintenance operations, with an OSHA (the Occupational Safety and Health Administration) permissible exposure limit of 5 $\mu g/m^3$.[4]

In 2009, the U.S. Department of Defense (DoD) issued a memorandum calling for the reduction of Cr(VI) across the DoD. In 2011, the DoD issued a final rule, amending the Defense Federal Acquisition Regulation Supplement (DFARS), to implement the requirements for minimizing the use of Cr(VI)-containing materials.[5] In 2016, the Strategic Environmental Research and Development Program (SERDP) and Environmental Security Technology Certification Program (ESTCP) Weapons Systems and Platforms Program Area have developed a strategy to reduce use of Cr(VI) by 90% or more at DoD maintenance depots over a period of five years (by the end of FY20).[6]

2.2 Past Research Focused on Hexavalent Chromium Replacements

Over the last 15 years, SERDP and ESTCP have made significant investments in fundamental research and technology demonstration and validation efforts of hexavalent chromium alternative technologies. As a result, several alternatives for Cr(VI) primers have been developed, such as: sacrificial coatings (magnesium- and aluminum-rich primers),[7] non-Cr(VI) primers containing alternative inhibitors, such as rare earth metals, as well as powder coatings and e-coats.[8] While sacrificial coatings can provide effective corrosion protection, they have their intrinsic limitations, such as the requirement of surface conductivity (not suitable for anodized aluminum alloys), lack of flexibility, and difficulties with paint removal and repair if the binder system is inorganic. Powder coatings and e-coats provide environmentally friendly alternatives for solvent-based systems, but lack the additional protection mechanisms for coating defects and damages. Organic coatings with inhibitor pigments are still needed for various aerospace applications. The following Cr(VI) replacements have been developed using several corrosion inhibitor chemistries: Inorganic inhibitors, including rare earths and magnesium oxide (MgO),[9] and organic inhibitors such as thiol (-SH) compounds and their combination with cation inhibitors.[10,11]

Some critical factors for the transition to Cr(VI)-free coating systems were identified by early fundamental research. For Cr(VI) primer alternatives, one critical requirement is to develop Cr(VI)-free inhibiting pigments "that are sufficiently soluble to provide high corrosion resistance without promoting osmotic blistering."[12] This statement echoes the opinion of industrial experts[13] and remains valid today. This is due to the significantly higher critical inhibitor concentration

required for non-Cr(VI) inhibitors to be effective. Cr(VI) compounds function as both cathodic and anodic inhibitors by reinforcing passivation at anodic sites while inhibiting the oxygen reduction reaction on cathodic sites. They are very effective as cathodic inhibitors, with a critical inhibition concentration of 0.001 mM, compared with 0.1 mM of other effective cathodic inhibitors, such as Cerium(III) and 2,5-dimercapto-1,3,4-thiadiazolate salt (tested in 5% salt solution).[14] This allows great flexibility in paint formulations with Cr(VI) for a wide range of applications. Traditional inhibitor pigments, such as inorganic anionic inhibitors, don't even come close to the efficacy of Cr(VI).[13] The low efficiency of non-Cr(VI) inhibitors often results in paint formulations with higher concentrations of inhibitors in their more soluble forms, which often have a detrimental effect on paint properties, resulting in high water permeability and/or blistering. Thiol organic compounds are being investigated as alternatives to Cr(VI) due to their well-known effectiveness as copper corrosion inhibitors.[14] However, thiol compounds, and some other important organic inhibitors, present another paint compatibility problems due to their solubility in the paint solvent and their reactivity with paint components. As a result, these organic inhibitors often interfere with the coating's curing process, resulting in a short pot life and inferior coating properties.

All of the above challenges are technical in nature, but they are seldom the only kind of challenge encountered. Besides the technical challenges associated with Cr(VI) replacements, there are also the challenges associated with the technology transfer and commercialization. The commercialization process of an alternative technology is surprisingly long[15] and not necessarily a linear process. The process can be very difficult and often becomes the "valley of death," a metaphor often used to describe the gap between innovative technologies and their commercialization. Although the valley of death suggests that technology transfer is about moving ideas from one entity to the next, technology transfer is about people in relationships.[16] As Doheny-Farina[17] and Coppola[18] suggested, technology transfer is about relationships and collaboration among individuals and groups (industry, government, and academia) with varied interests. A corrosion inhibitor is a special paint additive and its effectiveness can only be demonstrated in a coating formulation. In order to take NASA's new corrosion inhibitor technology to the field, a collaboration effort was established to include: the technology development team (NASA), a pigment/additive company (AMI), a paint formulator (PPG), and one of the end users (AFRL). This strategic collaboration was designed to move the technology towards commercialization.

In summary, developing Cr(VI) primer alternatives is a challenging process where two of the difficulties that have been identified are: (1) the inferior performance of non-Cr(VI) inhibitors and their paint compatibility problems, and (2) the complexities of the commercialization process. Encapsulation of non-Cr(VI) corrosion inhibitors allows their incorporation into primer formulations, in such a way that they are more effective, without having an adverse effect on the primer properties. A strategic collaborative effort between the technology development team, two industry partners, and a DoD end-user, was established to deal with the complexities of the commercialization process for this type of technological development in an effective manner.

2.3 Controlled-Release Inhibitors and Healing Agents as Alternatives to Cr(VI)

The development of encapsulation technology at NASA has progressed from the initial proof-of-concept work, in which a corrosion indicator was encapsulated into an oil-core (hydrophobic) microcapsule and shown to be delivered autonomously, under simulated corrosion

conditions, to a sophisticated portfolio of micro carriers (organic, inorganic, and hybrid) that can be used to deliver a wide range of active corrosion ingredients at a rate that can be adjusted to offer immediate as well as long-term corrosion control. The micro carriers have been incorporated into different coating formulas to test and optimize the autonomous corrosion detection, inhibition, and self-healing functions of the coatings.

The encapsulation technology developed by NASA (5 patents awarded and several filed) allows the incorporation of corrosion inhibitors into a primer in such a way that their delivery is triggered by the corrosion process itself. Encapsulation also allows the delivery of self-healing agents triggered by mechanical damage to the primer. The technology offers the versatility needed to include one or several corrosion control functions into the same primer to overcome the challenges of current alternatives to Cr(VI)-containing primers. The conceptual design is relatively simple: a multifunctional smart coating that uses micro-containers with a corrosion-controlled release mechanism triggered by the pH change at the onset of corrosion, as well as by mechanical damage. As illustrated in Figure 1, this technology enables the incorporation of different functions into a coating: early corrosion detection, corrosion protection, and self-healing. The functions that are relevant to this project are corrosion protection, using encapsulated corrosion inhibitors, and self-healing, using encapsulated self-healing agents. The technology allows the incorporation of these two different functions into a primer formulation.

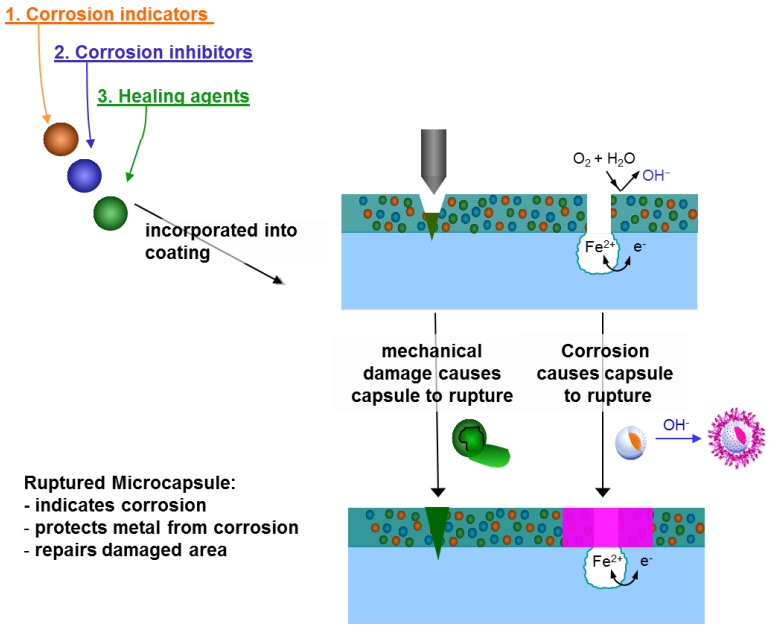

Figure 1. Smart Multifunctional Coating Concept.

2.3.1 Controlled-Release Inhibitor Micro Particles

Several microcapsules and micro particles formulas have been developed at NASA, tested, and optimized to incorporate the autonomous corrosion mitigation function into a primer. Experimental procedures were developed for the encapsulation of corrosion inhibitors into oil-core microcapsules, water-core microcapsules, and micro particles. Oil-core microcapsules, formed through an interfacial polymerization process, were developed to encapsulate organic inhibitors

and a few inorganic inhibitors. Water-core microcapsules, formed through interfacial polymerization, were developed to encapsulate water-soluble corrosion inhibitors. Micro particle formulations were developed to allow the incorporation of corrosion inhibitors, as solid particles, into a pH sensitive polymer matrix. Figure 2 shows SEM images of several microcapsules and micro particles developed by NASA.

This technology has been proven to be effective to address coating compatibility issues of both inorganic and organic inhibitors. Thiol (-SH)-based corrosion inhibitors, such as 2-mercaptobenzothiazole (2-MBT), have been encapsulated and incorporated into a high solids epoxy amine coating, at low inhibitor loading (5 wt%), and applied directly to bare AA2024 without pretreatment. ASTM B117[19] testing results showed significant corrosion protection at 4500 to 6000 hours (Figure 3). The benefit of encapsulation was also observed for effective inorganic anodic corrosion inhibitors with high water solubility. The encapsulation process made it possible to incorporate them into a coating formulation without causing blistering, while maintaining their corrosion protection function.

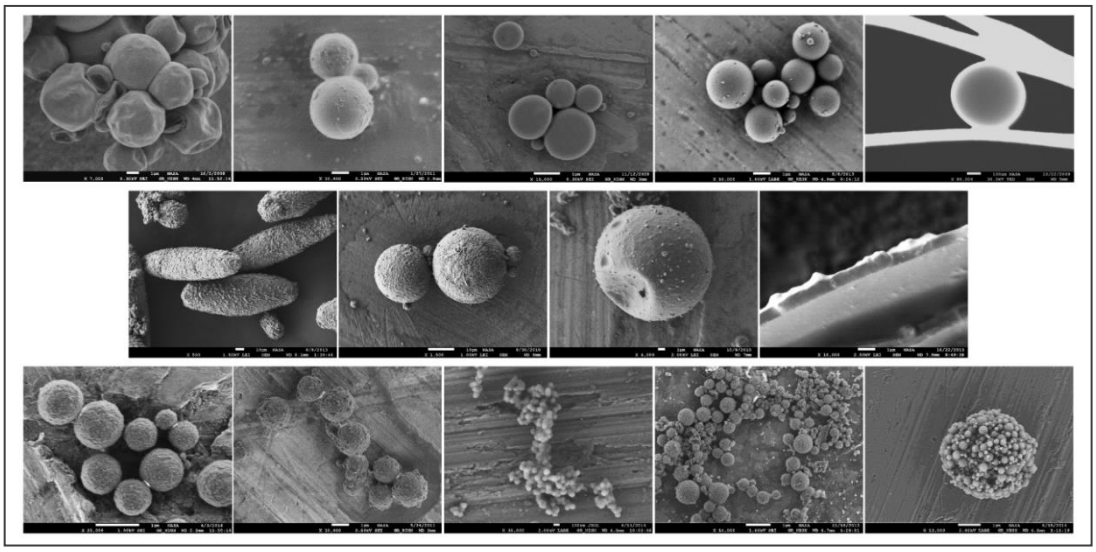

Figure 2. SEM images of microcapsules for indicator and inhibitors (first row); microcapsules for self-healing agents (second row), and organic and inorganic micro particles (third row).

While encapsulation has its obvious advantages as a controlled delivery system for corrosion inhibitors, such as improvement of coating compatibility, as it is the case for thiol compounds, and reduction of the inhibitor leaching rate (for longer corrosion protection), it is just an inhibitor delivery method. It cannot provide corrosion protection alone without the right inhibitor chemistry. The excellent corrosion protection results, shown in Figure 3, were obtained by incorporating encapsulated corrosion inhibitors into an experimental epoxy amine coating. Inhibitor C is a proprietary inorganic inhibitor that enhances the formation of the passive film on aluminum (anodic inhibitor) and 2-MBT is a cathodic inhibitor.

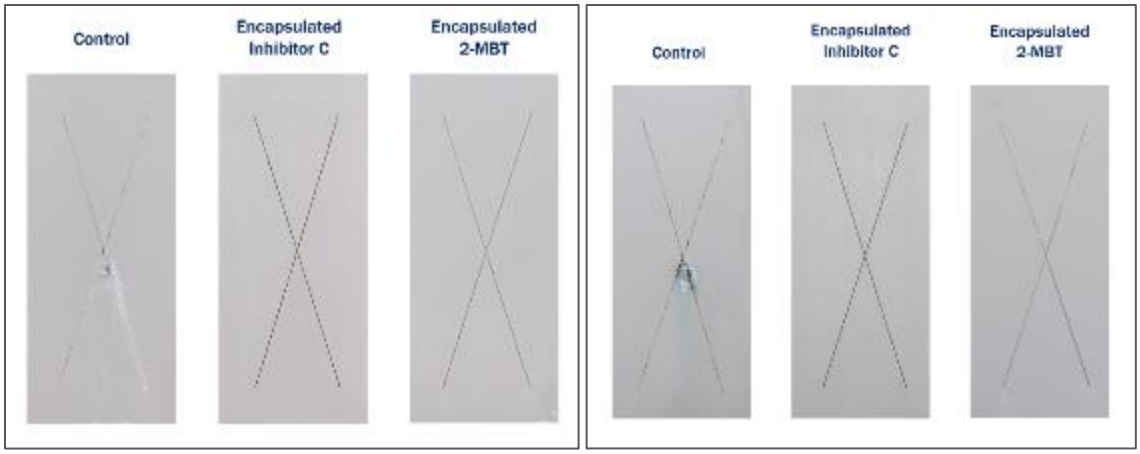

Figure 3. Epoxy-amine coating on aluminum alloy (no pretreatment) with encapsulated corrosion inhibitors): salt fog test results – 4500 hours (left three panels) and 6000 (right).

In addition to the smart-coating technology developers, our project team includes members who pioneered the development and scale-up of self-healing microcapsules and who were the first to successfully commercialize self-healing microcapsules, as coating additives, based on encapsulation technologies developed by scientists at the University of Illinois.[20] Self-healing coatings provide corrosion protection, at the coating damage sites, by releasing self-healing agents upon mechanical damage.[21]

In summary, the corrosion-triggered, controlled-release smart-coating technology developed by NASA overcomes the coating compatibility challenges of the alternative Cr(VI) inhibitors and has the potential to close the performance gap of non-Cr(VI) inhibitors. NASA's smart coating technology has been optimized at the lab-scale through the years. The encapsulation method and corrosion protection performance of encapsulated inhibitors have been improved sufficiently overtime. In order to take this technology out of the lab, technology readiness level (TRL) 4, and into the field for a DoD aerospace application (TRL 7), the microencapsulation process was scaled up prior to the follow on field demonstration and validation effort that was proposed to the FY18 ESTCP Topic B6: Demonstration/Validation of Alternatives to Hexavalent Chromium in Manufacturing and Maintenance of Weapons Systems proposal number WP-18-B6-5249).

2.3.2 Self-healing Microcapsules

The incorporation of self-healing functionality into a primer can be achieved by incorporating encapsulated self-healing agents into the primer. Mechanical damage to the primer ruptures the microcapsules to release the self-healing agents to repair the damaged area (Figure 4 and Figure 5). AMI has developed and commercialized an additive designed to improve the corrosion resistance of coating systems for steel and aluminum substrates by imparting self-healing functionality to one or more coating layers in the system.

AMI has commercialized self-healing microcapsules, as coating additives that can provide additional corrosion protection functionality to hexavalent chromium replacement primers.

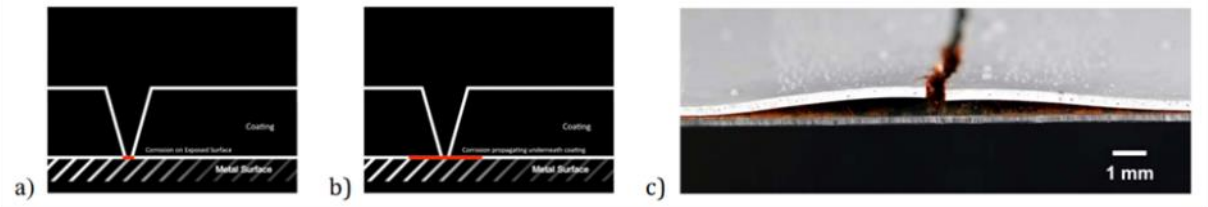

Figure 4. Schematic illustration of the effect of damage to a traditional coating: (a) the area exposed to the environment begins to rust, (b) over time the rust propagates underneath the coating (undercutting), and (c) undercutting of a polyurethane mastic coating on a cold-rolled steel substrate.

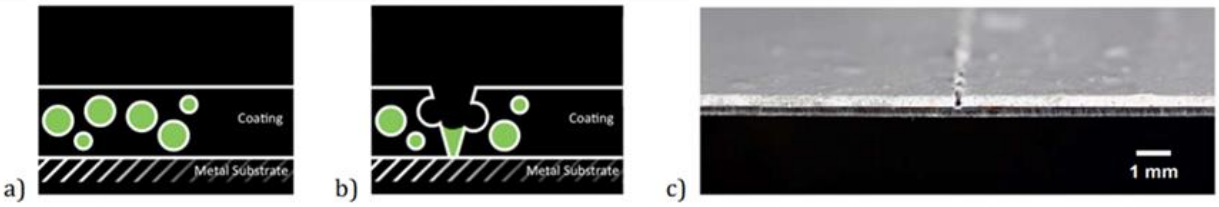

Figure 5. Schematic demonstrating a self-healing coating: (a) a coating containing encapsulated healing agent; (b) coating damage ruptures the microcapsules to release healing agent, and (c) polymerized healing agent restores protective function to a polyurethane mastic coating on a cold-rolled steel substrate eliminating undercutting.

3. MATERIALS AND METHODS

3.1 Self-healing Microcapsules

Self-healing microcapsules, containing a proprietary blend of healing agents, were provided by AMI. The microcapsules were prepared in an oil-in-water emulsion and were isolated to create a dry powder with a typical moisture content below 5 wt%. The self-healing microcapsules used for this project are branded as the AMPARMOR^{TM} 2000[22] product platform. This epoxy-based self-healing chemistry employs microcapsules with an average size of 10 microns. AMPARMOR^{TM} 2000 (Series 2) is recommended at a loading rate of between 2.5 wt% and 10 wt%, depending on the application, with a range of 5 wt% to 7.5 wt% most commonly employed. Loading rates of 2.5 wt% and 4.5 wt% were selected for this project.

3.2 Corrosion Inhibitor Micro Particles

2-MBT was selected as one of the corrosion inhibitors to be encapsulated into solid micro particles. The micro particles were about 1 micron in size and had the inhibitor dispersed throughout the pH-sensitive polymer matrix. A representative micro-particle synthesis process is shown in Figure 6 and a representative SEM image of 2-MBT micro particles is shown in Figure 7. The process starts by mixing two liquid phases to form a micro-emulsion. The two liquids involved are the water phase and the solvent phase. The water phase contains the pre-polymer for particle formation and the surfactants. The solvent phase contains a water-miscible solvent with active ingredient. In the case of an inhibitor particle, the synthesis process begins with dissolving the inhibitor into a water miscible solvent, such as ethanol or isopropanol; the inhibitor solution is then added to the water phase (the continuous phase). This process allows the inhibitor to be incorporated into the particle rather than being dissolved into the water. While the process is not

completely understood, it involves a somewhat spontaneous micro-emulsion process, similar to the Ouzo Effect,[23] but less stable, by which the inhibitor solution is dispersed into droplets. The polymerization reaction then occurs at the interfaces of these droplets which cause the inhibitor to be incorporated into particles before being dissolved into the water. Surfactants are used to control particle size and maintain particle distribution. Additional details on the encapsulation are provided in several patents.[24, 25, 26, 27, 28, 29] Loading rates of 2.5 wt% and 4.5 wt% were selected for this project.

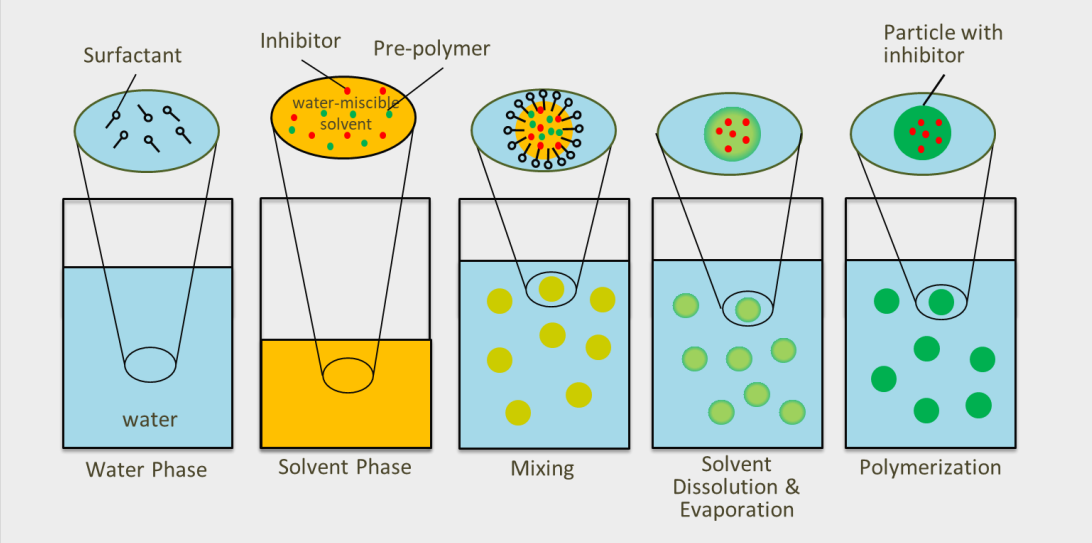

Figure 6. Schematic illustration of the procedure for encapsulating 2-MBT into micro particles.

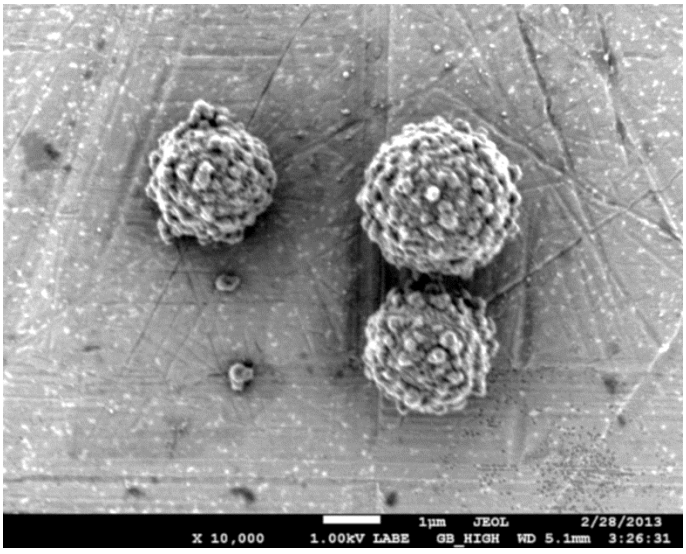

Figure 7. SEM image of micro particles with 2-MBT.

3.3 Scale Up of Microencapsulation

Two corrosion inhibitor microencapsulation procedures were selected for scaling up by AMI: 2-mercaptobenzothiazole (2-MBT) and 8-hydroxyquinoline (8-HQ). The target production of a small pilot scale was 2 kg of micro particles. The goal in both cases, as the process scale was increased, was to maintain the following key quality specifications and characteristics, which are important to the performance of the encapsulated inhibitors:

1. A target average size of 1 micron
2. Minimum agglomeration of resulting micro particles
3. A moisture content of the dried capsules of less than 5 wt%
4. Maximum core/shell ratio
5. Acceptable dispersion in target coating formulation

AMI started the scale-up processes of 2-MBT and 8-HQ micro particles with a thorough assessment of the initial laboratory-scale process. The assessment was designed to evaluate process parameters including surfactant type, surfactant concentration, process temperature profile, process duration and micro particle yield per batch. The surfactants included: Sodium dodecyl sulfate (SDS), gum, ethylene maleic anhydride (EMA), and polyvinyl alcohol (PVA). The micro particles were made of melamine formaldehyde pentaerythritol tetra (3-mercapto propionate) (MFPTT). N-methylpyrrolidone (NMP) and water were used as solvents. Viable micro particles from these trials were spray dried at 165 ºC. Selected samples were measured for particle size distribution for benchmarking. The reaction conditions used for the initial evaluation of the 2-MBT and 8-HQ encapsulation process are listed in Table 1 and Table 2, respectively. The moisture content of the micro particle samples was measured using a moisture analyzer (Sartorius MA35). The mass of the sample (1-2 g) was monitored when heated to and held at 60 ºC until no more mass change was detected (0 mg in 24 seconds).

Table 1. Experimental procedure details for the scale up of 2-MBT micro particle synthesis.

Reaction Label	Conditions (% = wt%)	Shell to 2-MBT Ratio	Water to 2-MBT Ratio	NMP to 2-MBT Ratio	Reaction Time (hours)	Result
MBT-R1	Standard Process SDS (2.5%) and Gum (5%)	3	75	8.33	5h at 65 ºC + 4h at 95 ºC	Dry powder
MBT-R2	SDS (2.5%)	3	75	8.33	5h at 65 ºC + 4h at 95 ºC	Unstable emulsion
MBT-R3	Gum (5%)	3	75	8.33	5h at 65 ºC + 4h at 95 ºC	Dry powder
MBT-R4	EMA (5%)	3	75	8.33	5h at 65 ºC + 4h at 95 ºC	Too stable for centrifugation. Static powder
MBT-R5	EMA (5%)	3	75	8.33	5h at 65 ºC	Too stable for centrifugation. Static powder
MBT-R6	SDS (2.5%) and Gum (5%) without active core	3	75	8.33	5h at 65 ºC + 4h at 95 ºC	Dry powder
MBT-R7	EMA (2.5%)	3	75	8.33	5h at 65 ºC + 4h at 95 ºC	Unstable emulsion
MBT-R8	PVA (5%)	3	75	8.33	5h at 65 ºC + 4h at 95 ºC	Dry powder
MBT-R9	EMA (2.5%) double impeller speed	3	75	8.33	5h at 65 ºC + 4h at 95 ºC	Unstable emulsion
MBT-R10	SDS (2.5%) and Gum (5%) double impeller speed	3	75	8.33	5h at 65 ºC + 4h at 95 ºC	Dry powder
MBT-R11	PVA (5%), 20% Solids, 50% 2-MBT	3		8.33	5h at 65 ºC + 4h at 95 ºC	Unstable emulsion
MBT-R12	EMA (2.5%) pH Adjusted to 4.5	3	75	8.33	5h at 65 ºC + 4h at 95 ºC	Sticky powder
MBT-R13	PVA (2.5%)	3	75	8.33	5h at 65 ºC + 4h at 95 ºC	Dry powder
MBT-R14	SDS (1.25%) and Gum (2.5%)	3	75	8.33	5h at 65 ºC	Dry powder
MBT-R15	PVA (2.5%)	3	75	8.33	5h at 65 ºC	Dry powder
MBT-R16	SDS (1.25%) and Gum (2.5%) 2X MFPTT-2-MBT blend	3	42	8.33	5h at 65 ºC	Dry powder
MBT-R17	PVA (2.5%) - 2X MFPTT-2-MBT blend	3	42	8.33	5h at 65 ºC	Unstable emulsion
MBT-R18	SDS (1.25%) and Gum (2.5%) 4X MFPTT-2-MBT blend	3	25	8.33	5h at 65 ºC	Dry powder.
MBT-R19	PVA (2.5%) 4X MFPTT-2-MBT blend	3	25	8.33	5h at 65 ºC	Unstable emulsion
MBT-R20	SDS (1.25%) and Gum (2.5%) 4X MFPTT-2-MBT blend 50% MFPTT in water, 25% 2-MBT in NMP	3	18	3	5h at 65 ºC	Dry powder.
MBT-R21	SDS (1.25%) and PVA (2.5%) 4X MFPTT-2-MBT blend 50% MFPTT in water, 25% 2-MBT in NMP	3	18	3	5h at 65 ºC	Unstable emulsion
MBT-R22	SDS (1.25%) and Gum (2.5%) 4X MFPTT-2-MBT blend 50% prepolymer in water, 25% 2-MBT in NMP - double impeller speed	3	18	3	5h at 65 ºC	Dry powder.
MBT-R23	2X water phase with SDS (1.25%) and PVA (2.5%) 4X MFPTT-2-MBT blend 50% MFPTT in water	3	35	3	5h at 65 ºC	Dry powder.

Table 2. Experimental procedure details for the scale up of 8-HQ micro particle synthesis.

Reaction Label	Conditions (% = wt%)	Shell to 8-HQ Ratio	Water to 8-HQ Ratio	DMF to 8-HQ	Reaction Time (Hours)	Observation
HQ-R1	SDS (2.5%) and Gum (5%)	1.6	37.5	4.2	5h at 65 °C and 4h at 90 °C	No agglomerates.
HQ-R2	SDS (2.5%) and Gum (5%)	1.6	37.5	4.2	5h at 65 °C	No agglomerates. Some crystals on the walls of the reaction vessel
HQ-R3	SDS (1.25%) and Gum (2.5%)	3.14	18	3	5h at 65 °C	Lot of large agglomerates. Lot of rod-like crystals
HQ-R4	SDS (1.25%) and Gum (2.5%)	1.6	9	3	5h at 65 °C	Lot of large agglomerates. Lot of rod-like crystals
HQ-R5	SDS (1.25%) and Gum (2.5%)	1.6	9	3	7h at 65 °C	Lot of large agglomerates. Lot of rod-like crystals
HQ-R6	SDS (1.25%) and Gum (2.5%)	1.6	25	3	7h at 65 °C	A few agglomerates precipitated at the bottom. Some crystals on the walls of the reaction vessel
HQ-R7	SDS (2.5%) and Gum (5%)	1.6	37.5	4.2	7h at 65 °C	No agglomerates. A few crystals on the walls the reaction vessel
HQ-R8	Std. SDS (1.25%) and Gum (2.5%)	1.6	19	3	7h at 65 °C	Some agglomerates. Some rod-like crystals
HQ-R9	SDS (1.65%) and Gum (3.3%)	1.6	21	3	8h at 70 °C	No agglomerates. Very few crystals on the walls of the reaction vessel
HQ-R10	SDS (1.65%) and Gum (3.3%)	1.6	25	3	7h at 70 °C	No agglomerates. Very few crystals on the walls of the reaction vessel

3.4 Primer Coating Formulations

3.4.1 MIL-PRF-23377 Compliance

While corrosion resistance is the most important property of a corrosion protective primer, there are other coating properties that are also important. Some are evaluated to assure long term corrosion protection against potential physical damage and chemical attack, in the actual real world service environments, such as adhesion, flexibility, water and fluids resistance; some are related with easiness of application and repair, such as mixing/dilution, application, drying time, and strippability; some are related with appearance (fineness of grind and surface appearance); while other tests are used to verify proper resin chemistry and resin curing of the binder component (viscosity, pot life, and solvent/cure test).

In a non-chromate corrosion protective primer, the chromate alternative components (the non-chromate corrosion inhibitor, or its equivalent component) should provide corrosion protection, but they must also demonstrate paint formulation compatibility so that all the important coating properties can be achieved. In this work, MIL-PRF-23377 was used to evaluate the material compatibilities of the encapsulated inhibitor/healing agents and to facilitate the optimization of the paint formulation.

Military specifications, such as MIL-PRF-23377, were derived from laboratory testing results to ensure that new product chemistries perform similarly to legacy chromate treatments/coatings. It covers a range of effective, yet manageable tests, for DoD coating evaluation, and can be used as an effective guide for new paint formulation development when used properly. However, it has been recognized by ESTCP, and it should be emphasized, that these specifications were originally developed for chromate systems. The variation between chromate primers and non-chromate primers are not fully reflected in specification testing.[30] They should be used as a means, not the end, of non-chromate corrosion protective coating systems. Specifically, non-chromate primers rely more on the pre-paint surface preparation performance than do chromate primers.[30] Current MIL-PRF-23377 allows qualification of non-chromate primers with a chromate conversion coating as surface pretreatment. This poses an increased technical risk when the non-chromate primer may potentially be combined with a non-chromate pretreatment. In order to address this risk, some additional tests, with a no-chromate pretreatment, such as PreKote, were included in this effort. These tests were beyond the scope of the SERDP directive but otherwise followed the procedure of MIL-PRF-23377. The details of the substrate/pretreatment choices is described in section 3.4.3.

3.4.2 Primer Selection

As mentioned earlier, MIL-PRF-23377 was used as a guide to evaluate the material compatibilities of the encapsulated inhibitor/healing agents and their effects on physical and chemical properties of the non-chromate paint formulation.

Two types of primers are selected for testing in this work: a solvent based epoxy and a polythioether primer. While the epoxy primer is the natural choice for MIL-PRF-23377 evaluation, the polythioether primer was included to address the need for a flexible chrome-free primer to mitigate the degradation of aircraft outer mold line (OML) materials, which is the most costly maintenance driver for the United States Air Force (USAF) weapon system applications[6] despite the fact that polythioether coatings do not meet MIL-PRF-23377.

The solvent-based epoxy primer containing a non-chromate inhibitor package, which was developed to meet MIL-PRF-23377, was provided by PPG. A paint formulation of the same epoxy system, without the inhibitor package, was also provided for incorporation of encapsulated corrosion inhibitors and self-healing agents, to make the paint formulation effort more efficient. This allowed the project team to focus on scaling-up the inhibitor encapsulation process. Similarly, a flexible polythioether primer, with and without its commercial inhibitor package, was provided by PPG. Encapsulated corrosion inhibitor and self-healing agents were incorporated into the primer formulations without the inhibitor package to formulate the new non-chromate primers. All four primer formulation were used for MIL-PRF-23377 testing, as shown in Table 3.

Table 3. Coatings included in MIL-PRF-23377 compliance testing.

Primer	Primer Label	Description
Polythioether	1	Polythioether Control: Polythioether chrome-free primer (with PPG inhibitor package).
	5	Polythioether chrome-free primer with encapsulated 2-MBT (2.5 wt%) and self-healing microcapsules (2.5 wt%)
Epoxy	10	Epoxy Control: Epoxy chrome-free primer (with PPG inhibitor package)
	14	Epoxy chrome-free primer with encapsulated 2-MBT (4.5 wt%) and self-healing microcapsules (4.5 wt%)

3.4.3 Substrates and Pretreatments

As described in section 3.4.1, the majority of tests in the MIL-PRF-23377 allows use of a chromate conversion coating as a pretreatment of the substrates. This poses a technical risk when the non-chromate primer may potentially be combined with a non-chromate pretreatment. In order to address this risk, some additional tests, with a no-chromate pretreatment, such as PreKote, were performed beyond the scope but otherwise following the procedure of MIL-PRF-23377.

Four types of test panels were used per MIL-PRF-23377 requirements:

A = 2024-T3 substrate with (chromate) conversion coating, 2024-T3/Alodine
B = 2024-0 substrate anodized, 2024-0/Anodize
C = 2024-T3 Alclad substrate deoxidized, 2024-T3/Alclad/deoxidized
D = 2024-T3 Alclad with (chromate) conversion costing, 2024-T3/Alclad/Alodine

Two new types of test panels were added in this study:

E = 2024-T3 with PreKote pretreatment, 2024-T3/PreKote
F = 2024-T3 without any pretreatment, 2024-T3 bare

For tests involving the polythioether primer, E type panels (2024-T3/PreKote) were used in place of the required A type panel (2024-T3/Alodine). E type panels were also used, instead of C type panels, for adhesion testing. This was done to test the effect of PreKote on adhesion on 2024-T3.

For tests involving the epoxy primer, E type panels were added to some tests where only A type panels are required. This was done to compare the effect of the non-chromate pretreatment with that of the chromate pretreatment. For adhesion testing, F type panels, 2024-T3 bare, were used to test the adhesion of the primer on 2024-T3 without any pretreatment.

Table 4. Comparisons of Panels (Substrate/Pretreatment) Choices: MIL-PRF-23377 and this project.

MIL-PRF-23377 Requirement	Test	Coating Systems	Pretreatment MIL-PRF-23377	Panel/ Pretreatment Tested with Epoxy	Panel/ Pretreatment Tested with Polythioether
Physical properties – Paint before and after mixing	Fineness of grind	Primer Paint	None	None	None
	Accelerated storage stability	Primer Paint	None	None	None
	Viscosity	Primer Paint	None	None	None
	Pot life	Primer Paint	None	None	None
Physical properties – film	Surface appearance	Primer	A (2024-T3/ Alodine)	A	E (2024-T3/ PreKote)
	Drying time	Primer	A	A	E
	Adhesion	Primer only Primer with topcoat	C (2024-T3/Alclad /deoxidized)	F (2024-T3 bare)	E
	Flexibility	Primer	B (2024-0/Anodize)	B	B
Resistance	Water	Primer only Primer with topcoat	A	A and E	E
	Salt-spray corrosion	Primer only Primer with topcoat	A	A and E	E
	Filiform corrosion	Primer with topcoat	D (2024-T3/Alclad/ Alodine)	D	D
	Solvent (cure)	Primer only	A	A	E
	Fluids: Lubricating oil hydraulic fluid	Primer only	A	A and E	E
Working Properties	Mixing/dilution	Primer Paint	None	None	None
	Application	Primer Paint	None	None	None
Toxicity	Health Hazard Assessment	Primer Paint	None	None	None
Strippability	Strippability	Primer only	A	A and E	E

3.5 MIL-PRF-23377 Testing

Table 5 shows the MIL-PRF-23377 requirements, qualification tests, test methods, and expected property or performance requirements for compliance for Type I (standard pigments), Class N (non-chromate based corrosion inhibitors) primer coatings that are relevant to this effort. The following sections describe the test methods in details.

Table 5. MIL-PRF-23377 qualification test requirements, methods, and expected property or performance.

MIL-PRF-23377 Requirements	Test	Test Method	Expected Property or Performance
Physical properties – Paint before & after mixing	Fineness of grind	ASTM D1210[31]	5 or greater on Hegman scale
	Accelerated storage stability		Greater than 14 days at (60 ± 3) ºC (140 ± 5) ºF
	Viscosity	ASTM D1200[32]	< 40 seconds through a #4 Ford cup, immediately after mixing
	Pot life	ASTM D1200	< 70 seconds through a #4 Ford cup, after mixing and storage in a closed container
Physical properties – film	Surface appearance		Admixed primer – no sag, run, or streak on a vertical surface. Dried film – smooth, uniform, free of irregularities. No orange peel from six feet away.
	Drying time	ASTM D5895[33]	Tack free within 5 hours; dry hard within 8 hours
	Adhesion	ASTM D3359[34]	No less than 4A
	Flexibility	ASTM D6905[35]	No less than 10% elongation
Resistance	Water		Deionized water (DI) immersion at (49 ± 3) ºC (120 ± 5) °F for 4 days without any wrinkling, blistering or other defects.
	Salt-spray corrosion	ASTM B117[19]	Better than 2000 hours
	Filiform corrosion	ASTM D2803[36]	Topcoated primer coating: All filaments < 1/4"; Majority <1/8"
	Solvent (cure)	ASTM D5402[37]	Withstand 50 passes of MEK rubbing
	Fluids: Lubricating oil hydraulic fluid	MIL-PRF-23699[38] MIL-PRF-83282[39]	No coating deficiency or loss of adhesion after: 24 hour immersion at (121 ± 3) ºC (250 ± 5) ºF 24 hour immersion at (65.5 ± 3) ºC (150 ± 5) ºF
Working Properties	Mixing/dilution		Blend homogenously, no separation within an hour
	Application		Capable of being applied by HVLP or electrostatic spray
Toxicity		Health Hazard Assessment	The primer coatings shall have no adverse effect on the health of personnel when used for its intended propose.
Strippability	Method A Method B	TT-R-2918[40] MIL-R-81294[41]	Minimum of 90% removal by one of the methods

3.5.1 Salt Spray ASTM B117 Corrosion Resistance

The corrosion resistance qualification test, using the salt-spray corrosion standard practice ASTM B117,[19] was planned to be carried out as an important part of the MIL-PRF-23377 compliance evaluation, but it was also used as a preliminary screening method for the material

compatibility between the encapsulated inhibitor and self-healing agents and the other coating components in the paint formulation. In this initial screening test, the encapsulated inhibitor and healing agents were incorporated into the epoxy and the polythioether primer separately and in combination, the resulted paint formulations were compared with the commercial formulations. It is worth noting that due to an unanticipated delay in the availability of the MIL-PRF-23377-qualified chrome-free epoxy primer, a different epoxy coating that was available in the lab at the time was used to perform the preliminary ASTM B117 test (Phase I) while waiting for the chrome-free epoxy primer to perform the originally planned ASTM B117 test (Phase II) and all the other MIL-PRF-23377 compliance tests.

3.5.1.1 ASTM B117 Test Method

The coated test panels were prepared following the instructions given in MIL-PRF-23377 section 4.5.8.1, subjected to 2000 hours of salt fog exposure testing, and rated using ASTM D 1654 Standard Test Method for Evaluation of Painted or Coated Specimens Subjected to Corrosive Environments[42] as a guideline (Table 6).

Table 6. Rating of failure at scribe.

ASTM D 1654 Rating Scale Representative Mean Creepage from Scribe		
Millimeters	**Approximate Inches**	**Rating Number**
0	0	10
Over 0.0-0.5	0- 1/64	9
Over 0.5-1.0	1/64-1/32	8
Over 1.0-2.0	1/32-1/16	7
Over 2.0-3.0	1/16-1/8	6
Over 3.0-5.0	1/8-3/16	5
Over 5.0-7.0	3/16-1/4	4
Over 7.0-10.0	1/4-3/8	3
Over 10.0-13.0	3/8-1/2	2
Over 13-16.0	1/2-5/8	1
Over 16	5/8-more	0

3.5.1.2 Phase I ASTM B117

The Phase I ASTM B117 tests were designed to investigate how the incorporation of self-healing microcapsules and encapsulated corrosion inhibitor, 2-MBT, singly and in combination, would affect the physical properties and the corrosion protection performance of the primer. The coatings that were included on this ASTM B117 test (Phase I) are shown in Table 7. Coating 1 was a fully inhibited flexible coating. Coating 2 was the same coating without the inhibitor package. Coatings 3-5 consisted of coating formulations that were prepared by incorporating 2.5 wt% self-healing microcapsules (coating 3), 2.5 wt% 2-MBT micro particles (coating 4), and a combination of both (2.5 wt% self-healing microcapsules and 2.5 wt% micro particles) into coating 2 (coating 5). Coating 6 was the 02GN084 chrome-free epoxy polyamide primer. Coating 7 was formulated by incorporating the self-healing microcapsules and the 2-MBT micro particles into

coating 6. Coatings 8 and 9 were prepared by applying a white polyurethane (PPG CA 8201) topcoat top to coatings 6 and 7.

Table 7. Coating formulations included in ASTM B117 test (phase I).

Primer Class	Primer ID	Coating ID	Description
Polythioether	1	1	Polythioether Control: Polythioether chrome-free primer (with PPG inhibitor)
	2	2	Polythioether Negative Control: Primer 1 without inhibitor
	3	3	Polythioether heal: Primer 2 with self-healing microcapsules (2.5 wt%)
	4	4	Primer 2 with 2-MBT micro particles (2.5 wt%)
	5	5	Primer 2 with self-healing microcapsules (2.5 wt%) and 2-MBT micro particles (2.5 wt%)
Epoxy	6	6	Epoxy Control (I): Epoxy chrome-free primer (02GN084)
	7	7	Primer 6 with self-healing microcapsules (2.5 wt%) and 2-MBT micro particles (2.5 wt%)
	6	8	Primer 6 with top coat polyurethane CA8201
	7	9	Primer 7 with top coat polyurethane CA8201

Three aluminum alloy AA2024-T3 test panels were coated with each of the coatings described in Table 7. Some of the panels were pretreated with PreKote while others were used, as provided by the manufacturer, with an Alodine pretreatment. Four sets of panels were also top coated with a polyurethane topcoat (CA 8201). Table 8 shows the coating systems and dry film thickness (DFT) for the AA2024-T3 test panels included in the ASTM B117 test (phase I).

Table 8. Coating systems and dry film thickness of ASTM B117 Phase I test panels.

Primer		Coating System			Dry film Thickness (DFT), mils			
Primer Class	**Primer ID**	**Coating System ID**	**Topcoat**	**Pretreatment**	**Panel 1**	**Panel 2**	**Panel 3**	**Average**
polythioether	**1**	**1**	None	PreKote	1.4	1.5	1.4	1.4
	2	**2**	None	PreKote	1.6	1.5	1.5	1.5
	3	**3**	None	PreKote	2.0	2.2	1.9	2.0
	4	**4**	None	PreKote	2.7	2.8	2.7	2.7
	5	**5**	None	PreKote	2.2	2.3	2.2	2.2
Epoxy	**6**	**6**	None	PreKote	1.5	1.4	1.4	1.4
				Alodine	1.7	1.6	1.5	1.6
		8	None	PreKote	3.4	3.8	3.8	3.7
				Alodine	3.6	3.9	3.6	3.7
	7	**7**	CA 8201	PreKote	2.2	2.2	2.0	2.1
				Alodine	1.8	1.9	1.9	1.9
		9	CA 8201	PreKote	4.0	3.9	3.7	3.9
				Alodine	3.7	4.0	3.9	3.9

3.5.1.2 Salt Spray ASTM B117 Test (Phase II)

For the phase II salt spray ASTM B117 test, as well as all the other MIL-PRF-23377 compliance tests, test panels were prepared using the primers described in Table 3. Three aluminum alloy AA2024-T3 test panels were coated with each coating system. Some of the panels were pretreated with PreKote while others were used, as provided by the manufacturer, with an Alodine pretreatment. Four sets of panels were also top coated with a polyurethane topcoat (CA 9800/F17925). Table 9 shows the coating systems and dry film thickness (DFT) for the AA2024-T3 test panels included in the ASTM B117 test (phase II).

Table 9. Panel Identification and dry film thickness of ASTM B117 test (Phase II).

Coating System				Dry film Thickness (DFT), mils			
Primer Class	**Primer ID**	**Topcoat**	**Pretreatment**	**Panel 1**	**Panel 2**	**Panel 3**	**Average**
Polythioether	**1**	None	PreKote	3.0	2.9	2.8	2.9
	5	None	PreKote	3.1	2.9	2.9	3.0
Epoxy	**10**	None	PreKote	1.5	1.7	1.6	1.6
			Alodine	1.5	1.4	1.2	1.4
		CA9800/ F17925	PreKote	4.6	4.6	4.4	4.5
			Alodine	3.1	4.0	3.2	3.4
	14	None	PreKote	1.8	1.6	1.7	1.7
			Alodine	1.7	1.7	1.5	1.6
		CA9800/ F17925	PreKote	2.6	3.3	3.2	3.0
			Alodine	3.2	3.0	3.2	3.1

3.5.2 Water Resistance

Three aluminum alloy AA2024-T3 test panels were coated with each of the coatings systems described in Table 10. Some of the panels were pretreated with PreKote while others were provided by the manufacturer with an Alodine pretreatment. Four sets of panels were also top coated with a polyurethane topcoat (CA9800/F17925). The test panels were immersed in in tank filled with DI water after it was allowed to equilibrate at (49 ± 3) °C [(120 ± 5) °F] overnight. The water immersion setup was covered, and the samples were allowed to dwell for the required four days. Two hours after removal from the water, the coated panels were examined for wrinkling, blistering or any other coating deficiency.

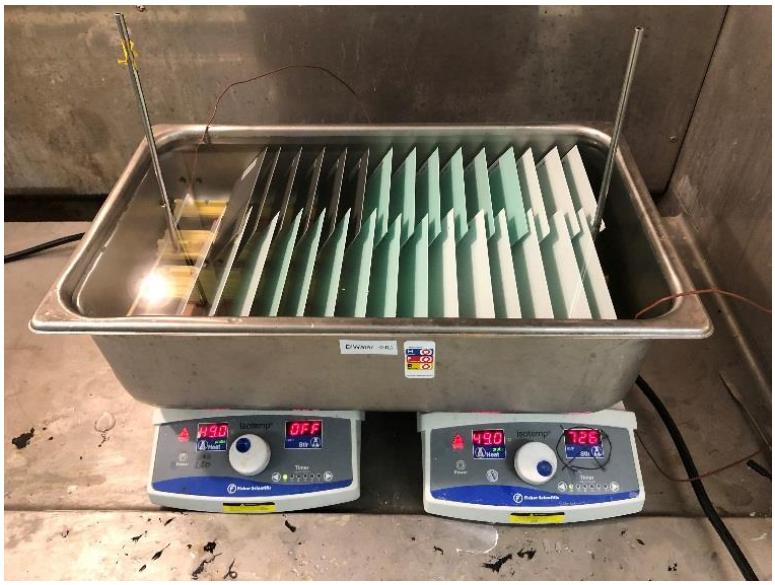

Figure 8. DI water immersion tank for MIL-PRF-23377 water resistance performance test.

Table 10. Coating systems included in the MIL-PRF-23377 water resistance performance test.

Primer Class	Primer Label	Topcoat	Pretreatment
Polythioether	**1**	None	PreKote
	5	None	PreKote
Epoxy	**10**	None	PreKote
			Alodine
		CA9800/ F17925	PreKote
			Alodine
	14	None	PreKote
			Alodine
		CA9800/ F17925	PreKote
			Alodine

3.5.3 Filiform Corrosion

Aluminum alloy AA2024-T3 test panels were coated with each of the coatings systems described in Table 11. The primer coatings were applied to clad and conversion coated test panels. System 1 and System 5 remained untopcoated. System 10 and System 14 were tested in a topcoated condition. Two intersecting lines were scribed diagonally across the coated surface of the test panels exposing the bare substrate. The test panels were then placed vertically in a desiccator containing approximately one inch of 12 Normal (N) hydrochloric acid (HCl) for 1 hour at room temperature so that only the HCl fumes came into contact with the sample. Within 5 minutes of removal from the desiccator, the test panels were placed in a humidity cabinet maintained at (40 ±

2) °C [(104 ± 3) °F] and relative humidity of (80 ± 5) percent for 1,000 hours. The test panels were then examined for conformance to the filiform corrosion resistance requirements.

Table 11. Coating systems included in the MIL-PRF-23377 filiform corrosion resistance test.

Primer Class	Primer Label	Topcoat	Panel/Pretreatment
Polythioether	**1**	None	Clad/Alodine
	5	None	Clad/Alodine
Epoxy	**10**	CA9800/ F17925	Clad/Alodine
	14	CA9800/ F17925	Clad/Alodine

3.5.4 Fineness of Grind

Hegman scale values for the primer coatings shown on Table 3 were obtained using a one-path Fineness of Grind Gage 54 (Precision Gage and Tool Co., 375 Gargrave Rd. Dayton, OH, 45449) was used to determine the Hegman scale value.

3.5.5 Accelerated Storage Stability

Accelerated storage stability test results on the chrome-free primers were provided by PPG. No accelerated storage stability test results on the flexible chrome-free primer were available from PPG.

3.5.6 Viscosity

Viscosity was determined using a #4 Ford viscosity cup filled level full with the coatings shown on Table 3 and measuring the time for the coating to flow through one of the standard orifices.

3.5.7 Pot Life

The primer coatings shown on Table 3 were mixed and stored in a close container for four hours. The pot life was determined by measuring the maximum viscosity of the unthinned coatings, using a #4 Ford viscosity cup filled level full and measuring the time for the coating to flow through one of the standard orifices.

3.5.8 Surface Appearance

The admixed primer coatings shown on Table 3 were applied to vertical panels and the appearance of the surface was observed visually after application and after the coating had dried.

3.5.9 Drying Time

The admixed primer coatings shown on Table 3 were applied to AA2024-T3 test panels and allowed to dry. Coatings 1 and 5 were applied to PreKote-treated panels. Coatings 10 and 14 were applied to PreKote as well as to Alodine treated panels. Dry-hard condition was evaluated, after 5 and 8 hours, by pinching the panels between the thumb on the film and forefinger on the back of the panel, with a relatively strong force, and observing if there was film displacement or notable marks left on the surface.

3.5.10 Adhesion

Triplicate aluminum alloy AA2024-T3 test panels for each of the of six coating systems were prepared and labeled for MIL-PRF-23377 adhesion testing as shown in Table 12. The test panels were immersed in distilled water for 24 hours at room temperature (Figure 9), removed from the water and wiped dry with a soft cloth. Within 3 minutes after removal from the water, two parallel scribes were made with a stylus through the coating to the substrate. The scribes were ¾ of an inch apart and 2 inches long. The panels were scribed to the substrate from opposing ends of the parallel scribes to form an "X". A 1-inch wide strip of masking tape (3M Company #250) was immediately applied with the adhesive side down across the scribes. The tape was pressed against the surface of the coating by passing a 4-1/2-pound rubber covered roller, approximately 3-1/2 inches in diameter and 1-3/4 inches in width across the tape eight times. The tape was removed with one quick motion and the X-cut area was examined for coating removal from the substrate or previous coating (for the top coated samples). The adhesion was rated using the scale given in ASTM Standard D 3359 – 97 and shown on Table 13. The coating damage was examined for conformance to the 3.7.4 paragraph (Adhesion) of MIL-PRF-23377.

Figure 9. Adhesion test panels immersed in DI water.

Table 12. Test panels for MIL-PRF-23377 adhesion testing.

Coating System				Panel Label
Primer Class	**Primer Label**	**Topcoat**	**Pretreatment**	**Panel Label**
Polythioether	**1**	None	PreKote	SYS 1 PK 1, 2, 3
	5	None	PreKote	SYS 5 PK 1, 2, 3
Epoxy	**10**	None	Bare	SYS 10 B 1, 2, 3
		CA9800/ F17925	Bare	SYS 10T B 1, 2, 3
	14	None	Bare	SYS 14 B 1, 2, 3
		CA9800/ F17925	Bare	SYS 14T B 1, 2, 3

Table 13. ASTM Standard D 3359 – 97 adhesion rating scale.

Rating	Description
5A	No peeling or removal
4A	Trace peeling or removal along incisions or at their intersection
3A	Jagged removal along incisions up to 1⁄16 in. (1.6 mm) on either side
2A	Jagged removal along most of incisions up to 1⁄8 in. (3.2 mm) on either side
1A	Removal from most of the area of the X under the tape
0A	Removal beyond the area of the X

3.5.11 Flexibility

Triplicate anodized aluminum alloy AA2024-0 test panels for each of the four primer coatings shown on Table 3 were prepared for flexibility testing, following the procedure described on section 4.5.5 of MIL-PRF-23377. A handheld coating thickness gauge (Positestor 6000) was used to measure coating thickness. The coating thickness (in mils) was recorded as the average of three readings that were taken along the vertical middle of the panel: top, middle, and bottom. The impact flexibility tester (Gardco) height weight/indenter was raised 42.5 inches (108 cm) from the test panel surface with the end, labeled A, facing the surface of the panel. The percent elongation, corresponding to the largest spherical impression at which no cracking occurs after dropping the weight/indenter of the test panel, was recorded using the technical data presented on Table 14 and examined for conformance to section 3.7.5 of MIL-PRF-23377.

Table 14. Technical data used to determine the percent area increase.[35]

Technical Data					
Spherical Segment	End	Base Diameter	Segment Radius	Segment Evaluation	% Area Increase
1	A	0.375	0.194	0.146	60
2	A	0.375	0.208	0.119	40
3	A	0.375	0.252	0.084	20
4	A	0.375	0.326	0.059	10

3.5.12 Solvent Resistance (Cure)

One aluminum alloy AA2024-T3 test panel, for each of the four primer coatings panels shown on Table 3, was prepared and labeled as shown on Table 15. The panels were marked with three 100 mm by 25 mm rectangular test areas (Figure 10). A cotton, terrycloth rag, soaked in methyl ethyl ketone (MEK) solvent, was used to rub each area back and forth 25 times (50 passes) within each marked area over the coating, with firm finger pressure in accordance with ASTM D5402 method A. The coating was examined for conformance to section 3.8.3 of MIL-PRF-23377.

Table 15. Test panels for MIL-PRF-23377 solvent resistance (cure) testing.

Primer Class	Primer Label	Surface Treatment	Panel Label
Polythioether	1	PreKote	SYS 1 PK
	5	PreKote	SYS 5 PK
Epoxy	10	Alodine	SYS 10 AL
	14	Alodine	SYS 14 AL

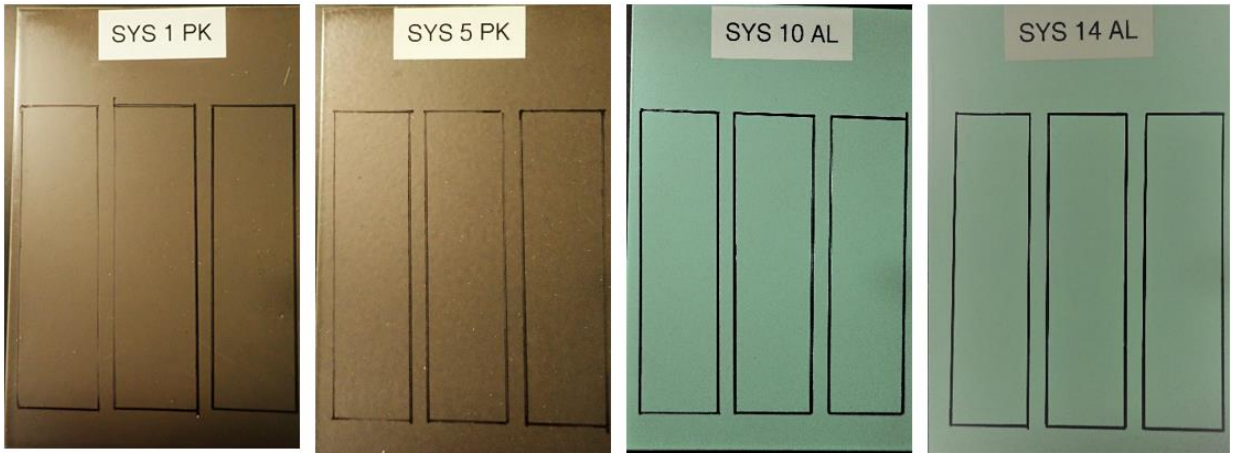

Figure 10. Test panels used for MIL-PRF-23377 solvent resistance (cure) testing.

3.5.13 Fluids Resistance: Lubricating, Hydraulic, Cleaning, and Deicing Fluids

In addition to the MIL-PRF-23377 fluid resistance requirement, described on section 3.8.4 of the specification, requiring testing the resistance to synthetic lubricating oil and to synthetic hydraulic fluid, direction from the Weapons Systems and Platforms Technical Committee required testing to provide evidence of resistance to alkaline cleaners and aircraft deicing fluids. Triplicate aluminum alloy AA2024-T3 test panels for each of the four primer coatings shown on Table 3 were prepared as shown on Table 16 for 24 hours immersion in synthetic lubricating oil conforming to MIL-PRF-23699, synthetic hydraulic fluid conforming to MIL-PRF-83282, Deicing/Anti Icing Fluid conforming to SAE AMS 1424/1, and Alkaline Cleaner/Degreaser conforming to SAE 1526A. The fluids used were: Lubricating Oil – Eastman Turbo Oil 2380 (121 ± 3°C); Hydraulic Fluid – Royco Hydraulic Fluid 782 (65 ± 3) °C; Deicing/Anti-Icing Fluid – Cryotech Polar Plus Type 1 (82 ± 3) °C – 63:37 Deicer to Water Mix; and Alkaline Cleaner/Degreaser – PTC-2001 (21 ± 3) °C – 3:1 Degreaser to water mix.

Table 16. Test panels for MIL-PRF-23377 lubricating oil and hydraulic fluid resistance testing.

Primer Class	Primer Coating	Surface Treatment	Panel Label
Polythioether	1	PreKote	SYS 1 PK
	5	PreKote	SYS 5 PK
Epoxy	10	PreKote	SYS 10 PK
		Alodine	SYS 10 AL
	14	PreKote	SYS 14 PK
		Alodine	SYS 14 AL

Four 2000 ml beakers were filled with the required fluids. The deicing fluid was mixed with a 63:37 deicer to water concentration. The alkaline cleaner was mixed with a 3:1 degreaser to water concentration. These are the maximum recommended working concentrations obtained from the manufacturer. Two panels from each triplicate set were placed in solution and allowed to dwell in the required solution for 24 hours as shown in Figure 11. Four hours after removal from the respective fluid, the coated panels were observed for occurrence of softening, blistering, loss of adhesion, or any other coating deficiency.

Figure 11. Experimental set up used for MIL-PRF-23377 lubricating oil and hydraulic fluid resistance testing.

3.5.14 Mixing/Dilution

The components of the chrome-free primer coatings shown on Table 3, including thinner if required, were mixed by a paint shaker in the volume mixing ratio specified by the manufacturer. Within one hour of mixing, the admixed coatings were observed visually for the presence of distinct layers.

3.5.15 Application

The components of the chrome-free primer coatings shown on Table 3 were applied using conventional, airless, high volume/low pressure (HVLP) equipment, apply the primer coating to test panels aiming to a dry film thickness of 15 to 23 µm (0.6 to 0.9 mil) for the chrome-free primer coating. The coatings were examined for conformance to sections 3.7.1 (surface appearance) and 3.9.2 (application) sections of MIL-PRF-23377.

3.5.16 Health Hazard Assessment

Composition and formulation information, of the encapsulated corrosion inhibitor 2-MBT, was provided to the Army Public Health Center for initial ecological and toxicity screening.

3.5.17 Strippability

Two sets of duplicate aluminum alloy AA2024-T3 test panels for each of the four primer coatings shown on Table 3 were prepared and labeled as shown on Table 17. One set was used for method A and the other one for method B (Figure 12) as described on section 4.5.13 of MIL-PRF-23377. A hydrogen peroxide paint stripper, (TT-R-2918A, product code PTS-202), was used for method A and a certified air marine & automotive MIL-R-81294D paint stripper (product code CCP-C282) was used for method B. Both paint strippers were procured from Products/Techniques, Inc., 3271 S. Riverside Ave., Bloomington, CA 92316.

Table 17. Test panels for MIL-PRF-23377 strippability testing.

Primer Class	Primer Coating	Surface Treatment	Panel Label
Polythioether	1	PreKote	A SYS 1 PK 1, 2
	5	PreKote	A SYS 5 PK 1, 2
Epoxy	10	PreKote	A SYS 10 PK 1, 2
		Alodine	A SYS 10 AL 1, 2
	14	PreKote	A SYS 14 PK 1, 2
		Alodine	A SYS 14 AL 1, 2

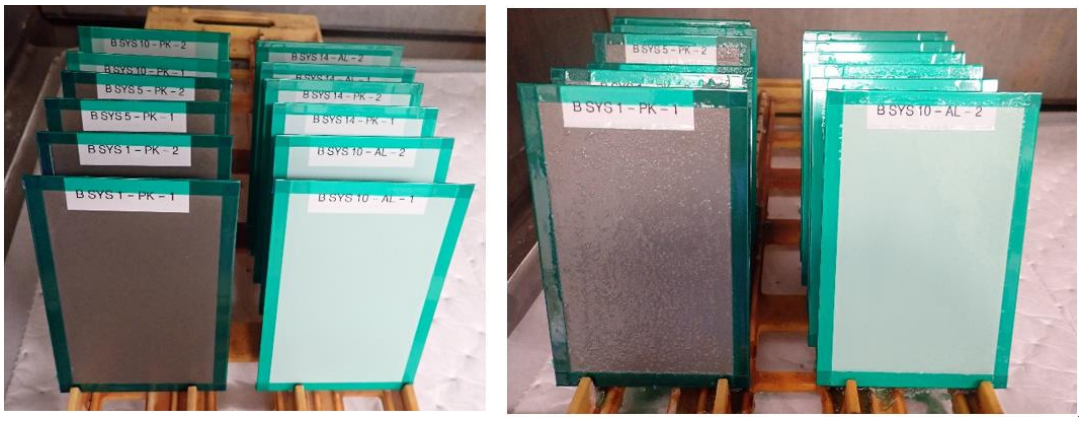

Figure 12. Test panels for MIL-PRF-23377 strippability testing (method B) before (left) and after application of paint stripper (right).

4. RESULTS AND DISCUSSION

4.1 Scaling Up of Micro Particle Synthesis Procedure

4.1.1 2-MBT Micro Particle Synthesis Scale Up

The effect of disparate surfactants on emulsion stability and processability was investigated. The selection of the best performing surfactant, at the lowest possible concentration,

improves the reaction process in three important ways: It results in a more robust process resistant to variability, affords the ability to accommodate more micro particles per batch, and allows for the elimination of the need to wash the micro particles before spray drying. The following surfactants were selected, based on their ability to stabilize viable micro particles: Ethylene maleic anhydride (EMA), polyvinyl alcohol (PVA) and sodium dodecyl sulfate (SDS)/gum Arabic in reactions labeled as MBT-R1 to MBT-R13 in Table 1; PVA at 2.5 wt % in reaction labeled as MBT-R13, and SDS/gum arabic at 1.25 wt %/2.5 wt% in reaction labeled MBT-R10.

The 4-hour heat treatment of the micro particles at 95 ºC was initially needed to treat unreacted functional groups on the surface of the micro particles that lead to agglomeration. This was a challenging step for scalability due to the energy demand coupled with the need to constantly add water to compensate for evaporation. Upon elimination of the heat treatment step in MBT-R14, dry particle size analysis showed particle sizes that were comparable to that of similar reactions which included heat treatment. Particle sizes for MBT-R1, MBT-R10 and MBT-R14 were measured to be (2 ± 1) µm. The removal of the heat treatment may have been possible due to increased mixing efficiency obtained by shifting from the magnetic stir bar, used in the lab-scale procedure (Figure 13), where the volume of the beaker is 2000 mL, to a hydrofoil impeller blade as shown in Figure 14 where the size of the reaction vessel shown is 10 gallons (37.9 L). Particle size distribution of selected dried 2-MBT micro particles are shown on Table 18.

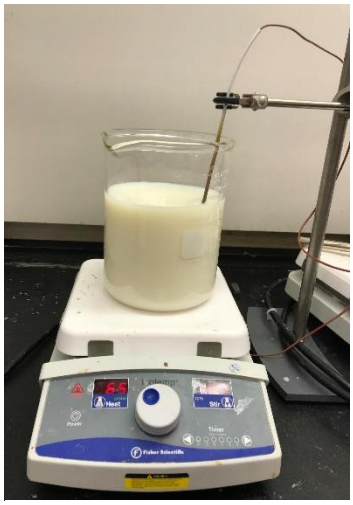

Figure 13. Laboratory scale procedure.

Increasing micro particle throughput was approached by increasing the MFPTT pre-polymer – 2-MBT solution mixture, decreasing the amount of water in the MFPTT) pre-polymer and decreasing the amount of N-methylpyrrolidone (NMP) in the 2-MBT solution. The amount of the MFPTT – 2-MBT mixture was doubled in MBT-R16 and MBT-R17 and was quadrupled in MBT-R18 and MBT-R19. Reactions MBT-R20 and MBT-R21 were similar to reactions MBT-R18 and MBT-R19 but the MFPTT pre-polymer and the 2-MBT solution were prepared at 50 wt% solids and 25 wt% solids respectively, compared to the original 24 wt% solids and 11 wt% solids. Reaction MBT-R22 was carried out in an effort to double the applied shear to MBT-R20 to drive down the particle size. Reaction MBT-R23 was used to address emulsion instability of higher MFPTT-2-MBT loading in reactions stabilized by PVA. At this stage, MBT-R16, MBT-R18, MBT-R20, MBT-R22 and MBT-R23 produced viable capsules, all of which exhibited particle sizes comparable to those obtained with the standard process MBT-R1 as shown in Table 18.

Figure 14. Setup for scaled-up synthesis of 4 kg of 2-MBT micro particle.

Table 18. Particle size distribution of selected dried 2-MBT micro particles

Reaction Label	Average Diameter (µm)	Standard Deviation
MBT-R1	1.84	1.03
MBT-R10	1.62	0.96
MBT-R14	1.67	1.07
MBT-R16	1.42	0.79
MBT-R18	1.53	0.49
MBT-R20	1.98	0.98
MBT-R22	2.05	1.09
MBT-R23	1.46	0.64

Analysis of the results obtained with all the process modifications lead to the selection of the reaction labeled as MBT-R20 (highlighted on Table 1) for the scale up process. This was due to the increased micro particle throughput of 15.3 wt% micro particles per batch, as opposed to the 4.6 wt% micro particles in the laboratory scale process MBT-R1. Since mixing, heating and, effectively, reaction dynamics change at increasingly larger scales, process trials at the 0.5 kg and 2.0 kg scales were needed. Ideally, equipment geometry, including ratios of the reaction vessel diameter (T), height (H), and hydrofoil impeller diameter (D) are to be as similar as possible during scale up. Realistically, reactions were performed using readily available equipment. The 0.1 kg and 0.5 kg batches were prepared without baffles. The 2 kg batch was upgraded to a 4 kg batch to reach a reasonable liquid height in a baffled 10 gallon (37.9 L) reaction vessel, with four evenly distributed 1.5-inch baffles, to avoid dead spots. Equipment dimensions were:

T : H : D = 12.4 cm : 15.2 cm : 6.4 cm (0.1 kg batch)
T : H : D = 15.3 : 21.6 cm : 11.4 cm (0.5 kg batch)
T : H : D = 35.6 cm : 38.1 cm : 11.4 cm (4 kg batch)

The agitation rate chosen at the 0.5 kg and 4.0 kg scales, at a minimum, matched or exceeded the impeller tip speeds used at the 0.1 kg scale but without causing solid body rotation or vortexing of the reactor contents. Despite the lack of complete geometric similarity, the 0.5 kg and 4.0 kg MBT-R20 batches successfully produced micro particles with sizes comparable to those of the 0.1 kg MBT-R20 batch and 0.1 kg MBT-R1 batch. The reagents and quantities used on the scaled up procedures are shown on Table 19. The mass of water is given as the sum of the mass of water needed to dissolve the surfactant and the mass of water needed to prepare the MFPTT pre-polymer.

Table 20 shows the reaction conditions, percent solids, and size of the particles obtained. Percent yield for the lab scale procedure (MBT-R1), the selected scale up procedure (MBT-R20), the 0.5 kg scaled up procedure, and the 4 kg scaled up procedure were 87%, 99%, 99%, and 93% respectively. The moisture content of the 2-MBT micro particles was 2.39%.

The scaling up of the microencapsulation process for 2-MBT to the small pilot scale of 2 kg of micro particles was achieved.

Table 19. 2-MBT Scale-up reagent quantities (g).

Reagents	MBT-R1 0.1 kg	MBT-R20 0.1 kg	MBT-R20 0.5 kg	MBT-R20 4 kg
Water	(600 + 75)	(300 + 25)	(1695 + 154)	(15356 + 1402)
Melamine	11.25	22.5	132.5	1202
Formalin	24	48	280.9	2548
PTT	8.2	16.26	95.1	1202
2-MBT	9	18	110	1000
NMP	75	54	330	3000
SDS	15	3.75	21.2	192.2
Gum Arabic	30	7.5	42.4	384.6

Table 20. 2-MBT Scale-up reaction details

Reaction Details	MBT-R1 0.1 kg	MBT-R20 0.1 kg	MBT-R20 0.5 kg	MBT-R20 4 kg
Reaction schedule	5h at 65 ºC and 4h at 90 ºC	6h at 65 ºC	6h at 65 ºC	6h at 65 ºC
Impeller / size (cm)	Hydrofoil/6.4	Hydrofoil/6.4	Hydrofoil/11	Hydrofoil/11
Mixing Rate (rpm)	650	650	389	500
Percent Solids (%)	4.4	15.3	15.3	15.3
Particle Size (μm)	(2 ± 1)	(2 ± 1)	(2 ± 2)	(2 ± 2)
Percent Yield	87	99	99	93

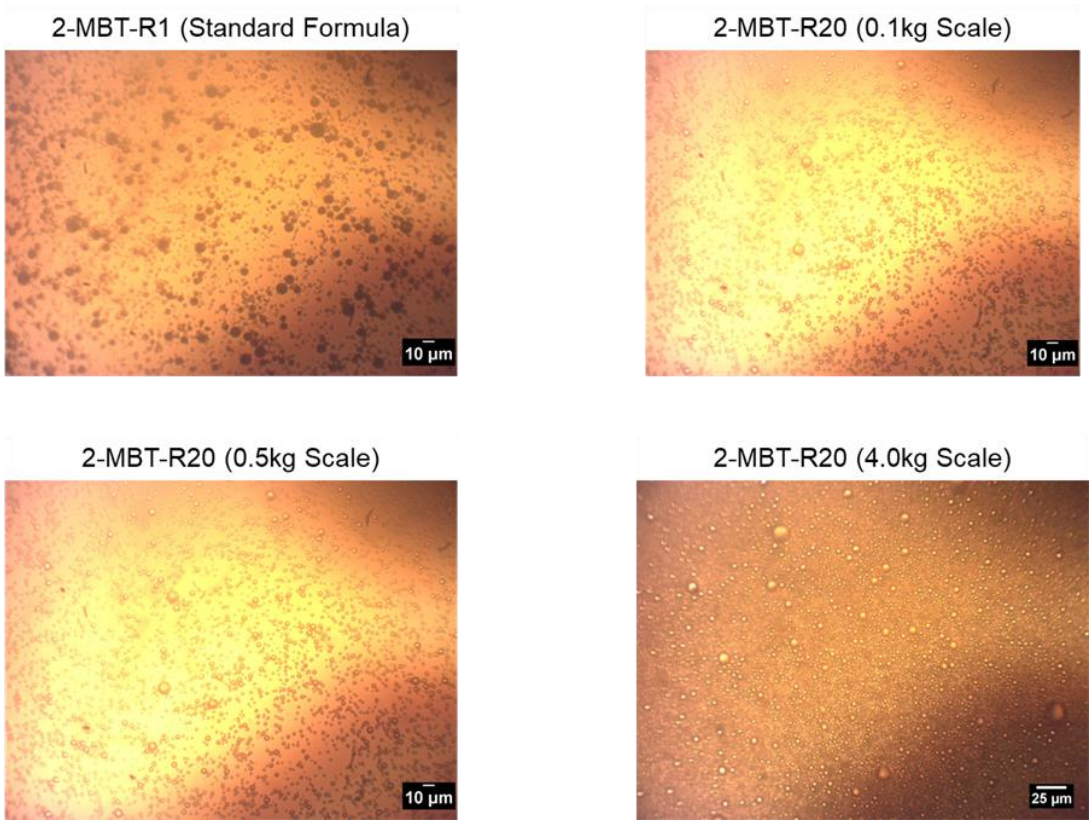

Figure 15. Optical microscopy images of 2-MBT micro particles obtained with reaction conditions labeled as 2-MBT-R1, 2-MBT-R20 (0.1 kg scale), 2-MBT-R20 (0.5 scale), and 2-MBT-R20 (4.0 kg scale) on Table 20.

4.1.2 8-HQ Micro Particle Synthesis Scale Up

The approach for the scale up of 8-HQ micro particle synthesis was similar to that for 2-MBT. Steps were taken to optimize surfactant level of addition, eliminate the 4 hour 95 ºC heating stage and increase micro particle yield per batch without compromising required specifications of the final product. A summary of the reaction conditions evaluated with a view towards selecting the most optimal conditions for scale up is provided in Table 2. HQ-R1 represents the standard laboratory scale reaction in which the concentration of SDS and Gum Arabic were 2.5 wt% and 5 wt% respectively. Additionally, similar to the MBT-R1 reaction conditions discussed earlier, the temperature profile of HQ-R1 incorporates a second step involving heating at 90 °C for 4 hours. In HQ-R2, the reaction conditions were kept the same as those for HQ-R1 except for the exclusion of the second heating step (90 ºC for 4 hours). This reaction was performed to assess the effect of the second heating step. At the end of HQ-R2, some crystal formation was observed on the walls of the reaction container. In parallel to HQ-R2, another reaction, HQ-R3, was run using conditions identical to that of the reaction selected for the scale up of 2-MBT micro particle production (MBT-R20). However, these reaction conditions were found to be unsuitable for the scaled up synthesis of 8-HQ micro particles due to the formation of large agglomerates and rod-like crystals. The reactions HQ-R4 (which including heating at 65 °C for 5 hours) and HQ-R5 (which included heating at 65 °C for 7 hours) were performed to understand the effect of process duration. Similar to the observations made for reaction HQ-R3, both reactions HQ-R4 and HQ-R5 resulted in the formation of large agglomerates and rod-like crystals. As such, HQ-R6 was run with a lower

theoretical micro particle batch yield (percent solids). Lowering the percent solids while keeping surfactant concentration at the same level led to a reduction in the formation of agglomerates and crystals.

Reactions HQ-R1, HQ-R3, and HQ-R7 exhibited different temperature profiles and of these three, only HQ-R1 resulted in crystal-free product. Since HQ-R1 was the only condition that employed the second heating step, the lack of crystal formation in this reaction mixture led to a hypothesis that elevated temperature and likely longer process times could minimize or prevent crystal formation. As such, the reaction temperature and duration were increased for HQ-R9 and HQ-R10 to 70 °C for 8 hours. When HQ-R8 and HQ-R9 were compared, with the same total amount of theoretical percent solids, HQ-R9 conditions which included a higher amount of surfactant prevented the formation of agglomerates, while agglomeration of particles was observed for HQ-R8. Reactions labeled HQ-R9 and HQ-R10 produced similar results with no agglomeration of particles observed in either. Since HQ-R9 (highlighted on Table 2) contained a higher amount of percent solids, it was selected for the scale-up process to increase efficiency.

A 0.5 kg batch (HQ-R11) was produced en route to the 2 kg production (HQ-R12) batch to ensure no adverse effects caused by increasing the scale. The full-scale (2 kg) reaction (HQ-R12) was successful with comparable results to HQ-R9 and HQ-R11 (Table 2). The experimental setup of this scale-up reaction was identical to that used for the 4 kg batch of MBT-R20 (Figure 14).

The slurries resulting from reactions HQ-R1, HQ-R9, HQ-R11, and HQ-R12 were spray dried at an inlet temperature of 165°C to obtain dry powder. A small quantity of dry powder of each sample was re-dispersed in de-ionized water, sonicated for 10 minutes, and imaged using optical microscopy. The images of these samples are shown in Figure 16. Overall, the dried particles of all these samples appeared to show good dispersion in de-ionized water.

Table 21 shows the quantities of the reagents used in the scale up process for 8-HQ.

Table 22 shows the reaction conditions, percent solids, size of the particles obtained, and percent yield. The moisture content of the 8-HQ micro particles was 2.94%. The average micro particle size was 2 µm. Although a target of 1 µm was initially set, the particle size obtained at optimized production conditions is considered compatible with targeted primer applications. This was confirmed by performing experiments in which the micro particles were incorporated in both solvent-borne (4-5 mils dry) and water-borne (2-3 mils dry) coatings. No dispersion problems were observed. It is anticipated that a size less than 3 µm should not be a problem for aerospace primers at 12.5 to 25 µm.

The scaling up of the microencapsulation process for 8-HQ to the small pilot scale of 2 kg of micro particles was achieved.

Table 21. 8-HQ Scale-up reagent quantities (g).

Reagents	HQ-R1 0.1 kg	HQ-R9 0.1 kg	HQ-R11 ~0.5 kg	HQ-R12 2 kg
Water*	(600 + 75)	(250 + 25)	(2500 + 250)	(16980 + 1709)
Melamine	11.25	8.125	81.2	554.4
Formalin	24	17.3	172.8	1182
PTT	8.2	5.87	58.7	400.4
8-HQ	18	13	130	887.5
DMF	75	39	390	2662.5
SDS	15	4.125	41.25	280
Gum Arabic	30	8.25	82.5	560
*Sum of mass of water needed to dissolve the surfactant and mass of water needed to prepare the MFPTT pre-polymer.				

Table 22. 8-HQ Scale-up reaction details.

Reaction Details	HQ-R1 0.1 kg	HQ-R9 0.1 kg	HQ-R11 ~0.5 kg	HQ-R12 2 kg
Reaction schedule	5h at 65 ºC + 4h 90 ºC	8h at 70ºC	8h at 70ºC	8h at 70ºC
Mixer type/blade	Hydrofoil/2.5”	Hydrofoil/2.5”	Hydrofoil/4.5”	Hydrofoil/4.5”
Mixing rate	650rpm	650rpm	250rpm	390rpm
Percent Solids (%)	6.8	12.1	12.1	12.1
Particle size (µm)	(2 ± 1)	(2 ± 1)	(2 ± 1)	(2 ± 2)
Percent Yield	80	78	81	77

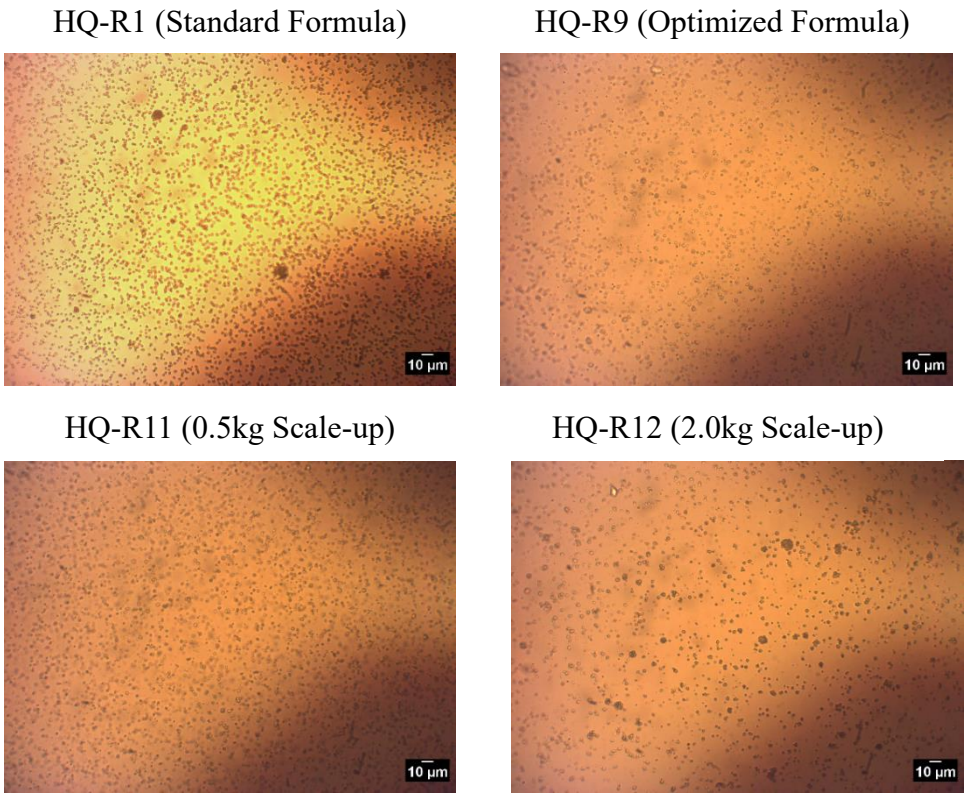

Figure 16. Optical Microscopy images of 8-HQ micro particles obtained using procedures labeled as HQ-R1, HQ-R9, HQ-R11, and HQ-R12 on Table 22.

4.2 Moisture Content and Micro particle Size

After spray-drying, the moisture content values for the 2-MBT and 8-HQ micro particles were recorded at 2.39% and 2.94% respectively, thus meeting the key quality specification of a moisture content of the dried capsules of less than 5 wt%. The average size of the 2-MBT and 8-HQ micro particles, which was achieved with minimal particle agglomeration, was less than 2.4 microns. Although a target of 1 micron was initially set, the particle size obtained at optimized production conditions is considered compatible with targeted primer applications.

4.3 MIL-PRF-23377 Test Results

4.3.1 B117 Phase I Test Results

The MIL-PRF-23377 specification for corrosion resistance, based on the B117 salt spray test, requires that "the primer coatings, with and without a topcoat, shall not exhibit blistering, lifting of either coating, nor substrate pitting after exposure to a 5 percent salt spray for 2000 hours. There shall be no white corrosion or pitting in the scribe." The panels from the B117 Phase I test (Table 7) were analyzed after 2000 hours of salt fog exposure and are shown in Figure 17 to Figure 29. Table 23 shows the ASTM D1654 ratings for the panels.

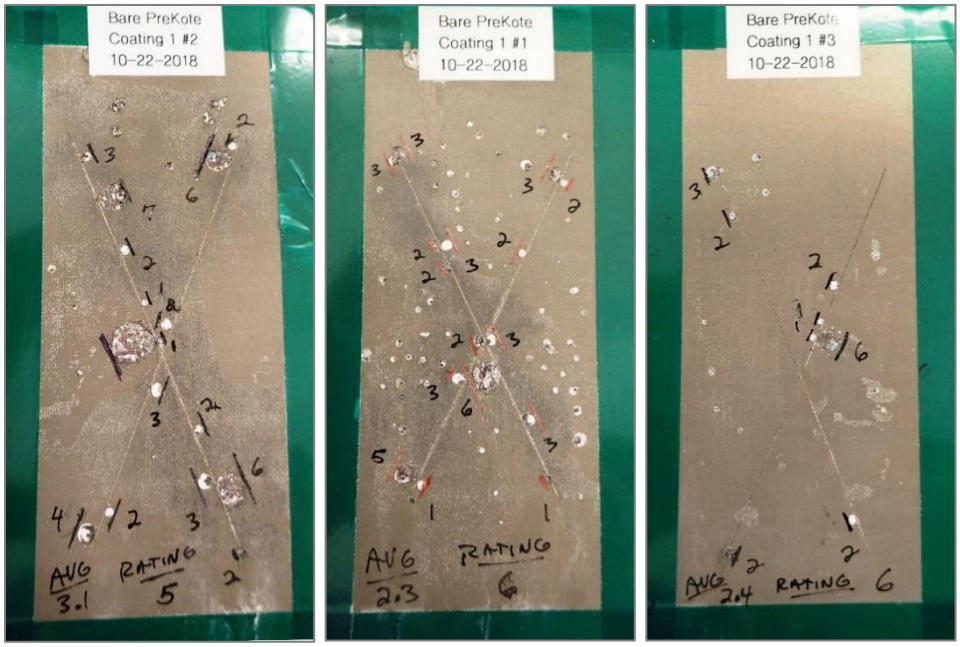

Figure 17. Coating 1 on AA2024-T3 panels with PreKote pretreatment after 2000 hours of salt fog exposure showing ASTM D1654 ratings with an average of 6.

Figure 18. Coating 2 on AA2024-T3 panel with PreKote pretreatment after 2000 hours of salt fog exposure showing ASTM D1654 ratings with an average of 6.

Figure 19. Coating 3 on AA2024-T3 panel with PreKote pretreatment after 2000 hours of salt fog exposure showing ASTM D1654 ratings with an average of 7.

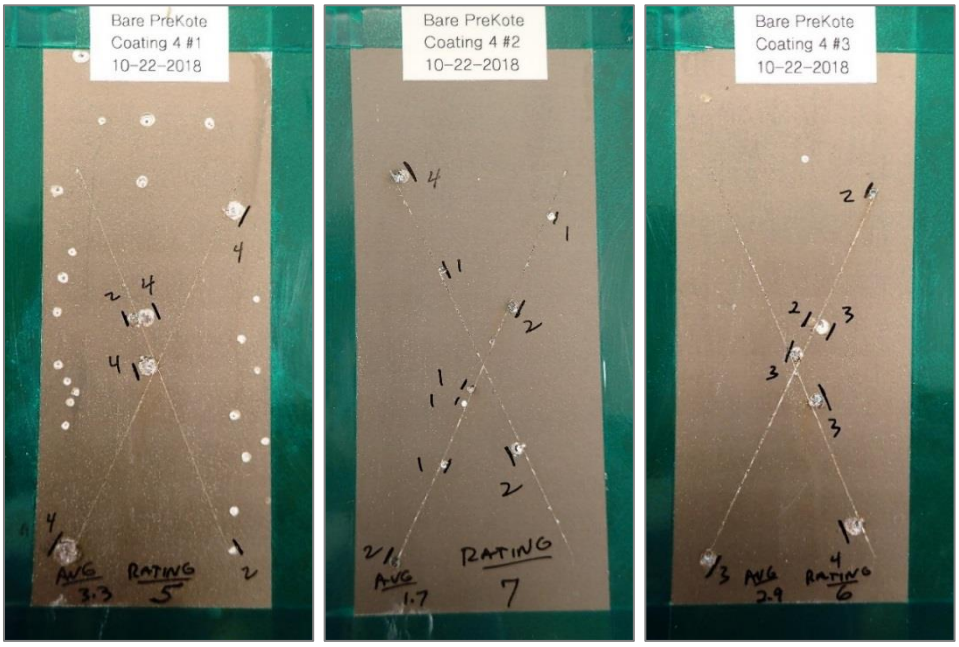

Figure 20. Coating 4 on AA2024-T3 panel with PreKote pretreatment after 2000 hours of salt fog exposure showing ASTM D1654 ratings with an average of 6.

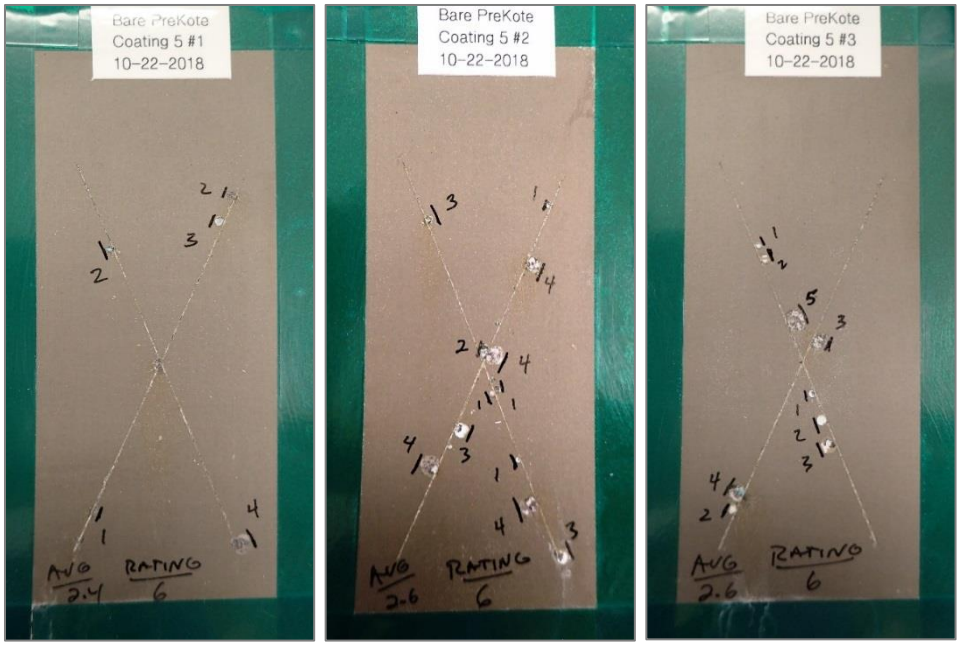

Figure 21. Coating 5 on AA2024-T3 panels with PreKote pretreatment after 2000 hours of salt fog exposure showing ASTM D1654 ratings with an average of 6.

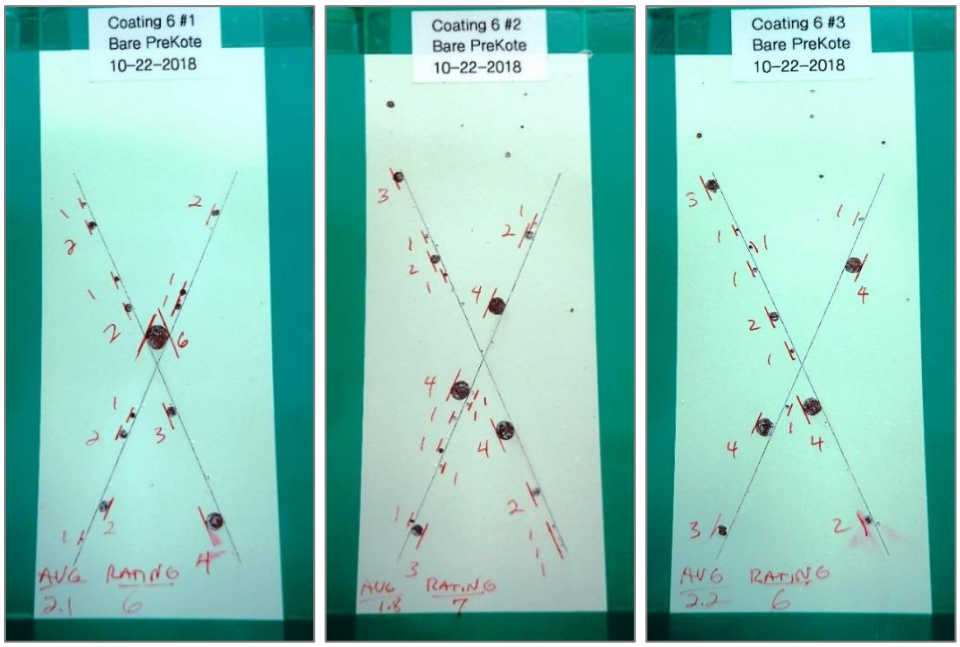

Figure 22. Coating 6 on AA2024-T3 test panels with PreKote pretreatment after 2000 hours of salt fog exposure showing ASTM D1654 ratings with an average of 6.

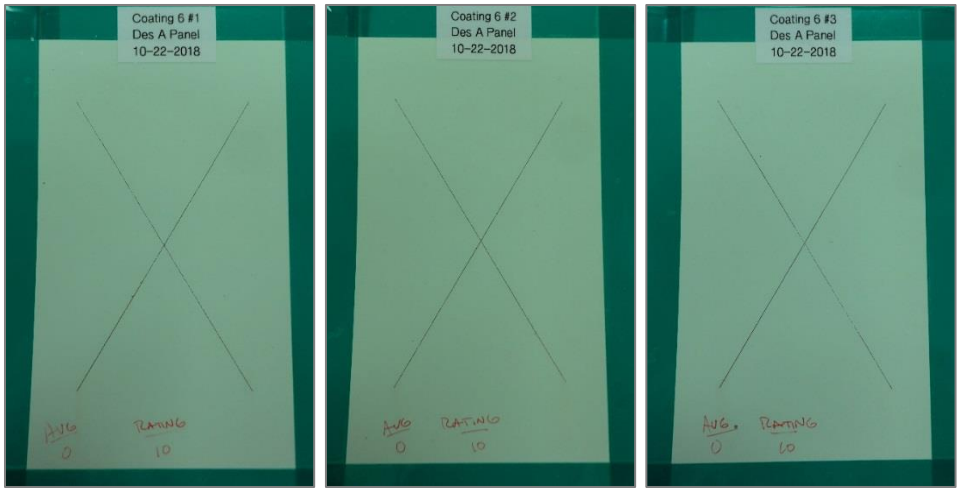

Figure 23. Coating 6 on AA2024-T3 test panels with Alodine pretreatment after 2000 hours of salt fog exposure showing ASTM D1654 ratings with an average of 10.

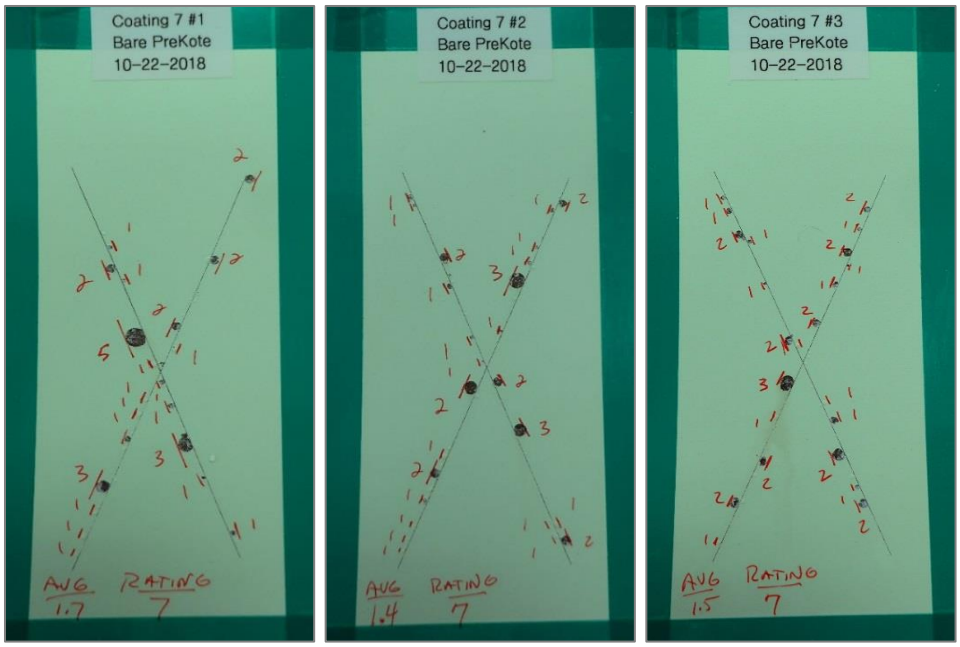

Figure 24. Coating 7 on AA2024-T3 test panels with PreKote pretreatment after 2000 hours of salt fog exposure showing ASTM D1654 ratings with an average of 7.

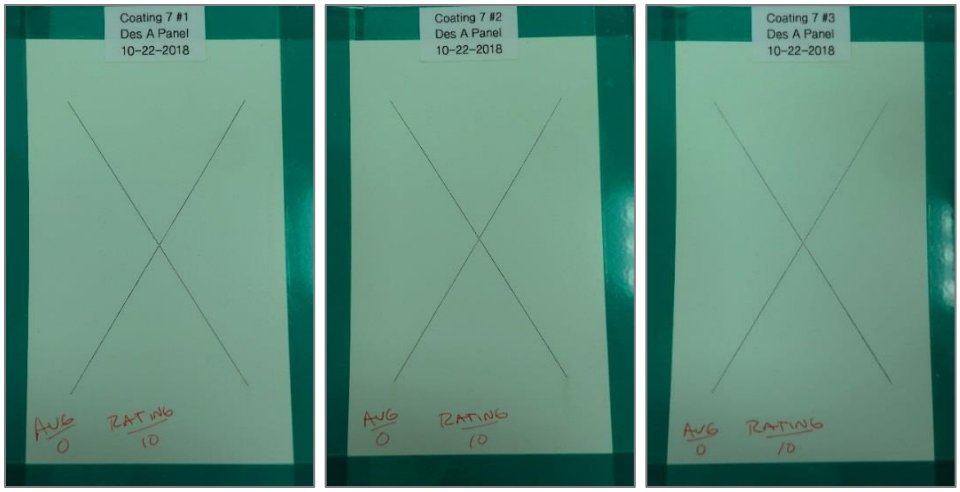

Figure 25. Coating 7 on AA2024-T3 test panels with Alodine pretreatment after 2000 hours of salt fog exposure showing ASTM D1654 ratings with an average of 10.

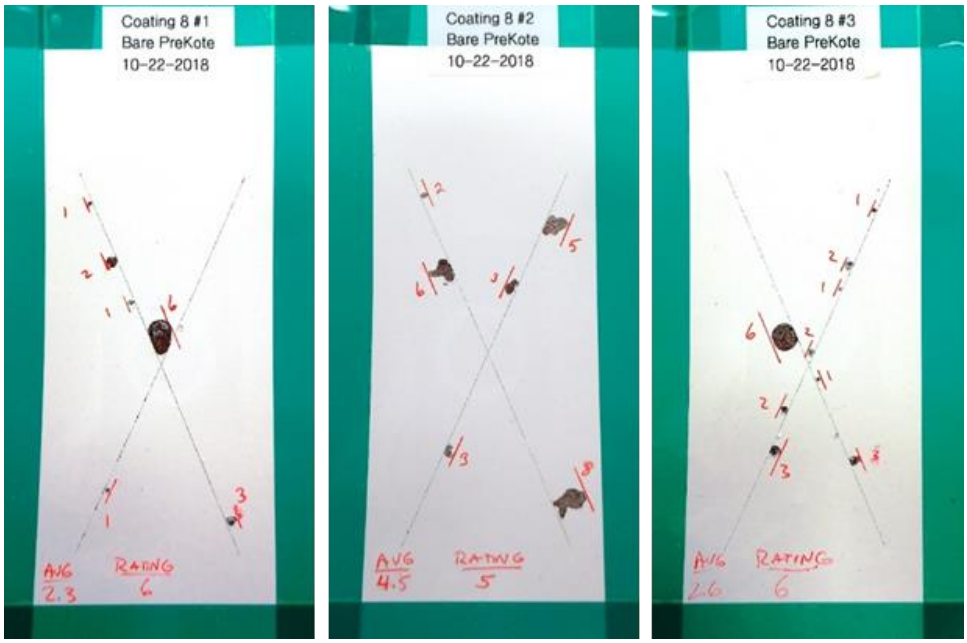

Figure 26. Coating 8 on AA2024-T3 test panels with PreKote pretreatment after 2000 hours of salt fog exposure showing ASTM D1654 ratings with an average of 6.

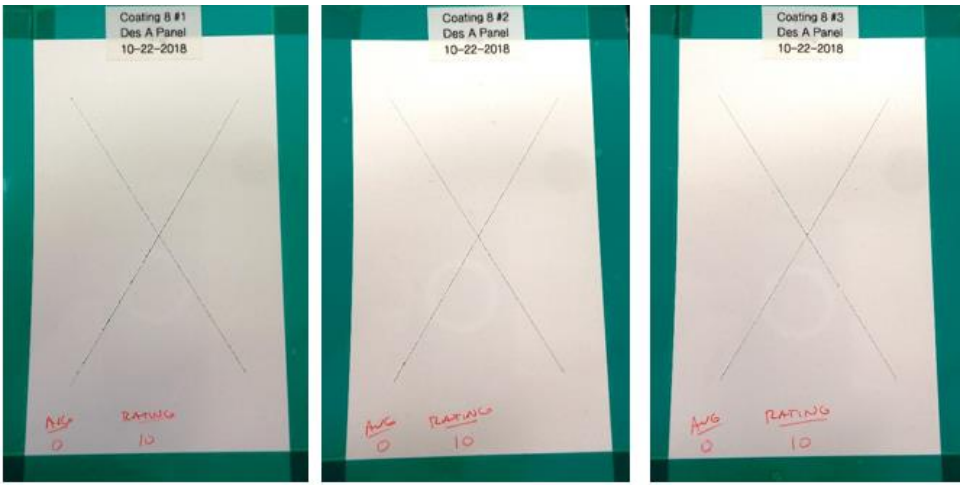

Figure 27. Coating 8 on AA2024-T3 test panels with Alodine pretreatment and CA 8201 polyurethane topcoat after 2000 hours of salt fog exposure showing ASTM D1654 average rating of 10.

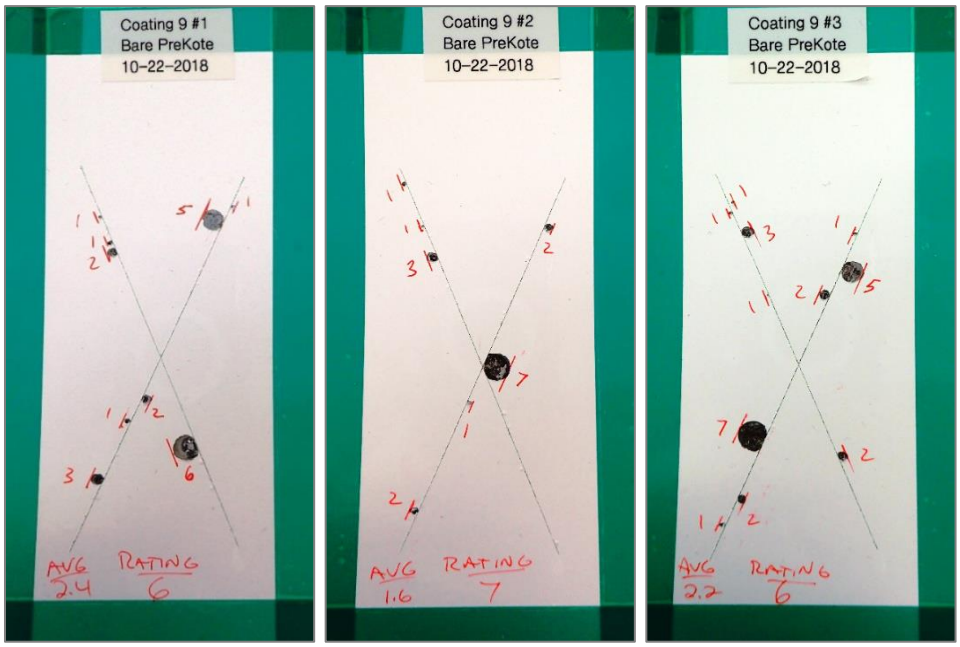

Figure 28. Coating 9 on AA2024-T3 test panels with PreKote pretreatment and CA 8201 polyurethane topcoat after 2000 hours of salt fog exposure showing ASTM D1654 ratings with an average of 6.

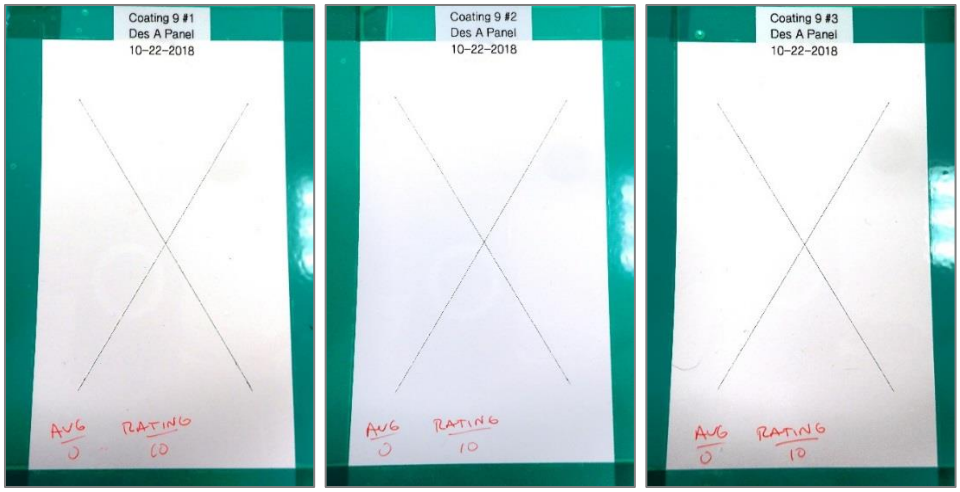

Figure 29. Coating 9 on AA2024-T3 test panels with Alodine pretreatment and CA 8201 polyurethane topcoat after 2000 hours of salt fog exposure showing ASTM D1654 average rating of 10.

Table 23. ASTM D1654 ratings of B117 Phase I test panels.

Coating System					Mean Creepage from Scribe				
Primer Class	**Primer Label**	**Description**	**Topcoat**	**Pretreat-ment**	**Panel 1**	**Panel 2**	**Panel 3**	**Average**	**Rating**
Polythioether	1	Control (fully inhibited)	None	PreKote	2.3	3.1	2.4	2.6	6
	2	Control (uninhibited)	None	PreKote	2.9	2.7	1.9	2.5	6
	3	With 2.5 wt% self-healing microcapsules	None	PreKote	1.6	2	2.7	2.1	7
	4	With 2.5 wt% 2-MBT micro particles	None	PreKote	3.3	1.7	2.9	2.6	6
	5	With 2.5 wt% self-healing microcapsules and 2.5 wt% 2-MBT micro particles	None	PreKote	2.4	2.6	2.6	2.5	6
Epoxy	6	Epoxy Control (I)	None	PreKote	2.1	1.8	2.2	2.0	6
				Alodine	0.0	0.0	0.0	0.0	10
			CA 8201	PreKote	2.3	4.5	2.6	3.1	6
				Alodine	0.0	0.0	0.0	0.0	10
	7	Epoxy Control (I) with 2.5 wt% self-healing microcapsules and 2.5 wt% 2-MBT micro particles	None	PreKote	1.7	1.4	1.5	1.5	7
				Alodine	0.0	0.0	0.0	0.0	10
			CA 8201	PreKote	2.4	1.6	2.2	2.1	6
				Alodine	0.0	0.0	0.0	0.0	10

This phase I B117 testing provided some informative results on the effect of the encapsulated 2-MBT inhibitor and the self-healing microcapsules on the polythioether and on the epoxy primer tested.

For the epoxy primer systems, the pretreatment was the predominant factor that determined the outcome of the test. Both the epoxy primers, 6 and 7, with or without the topcoat, passed the salt fog resistance requirement when tested with the Alodine chromate pretreatment. They both failed the salt fog test, with a similar rating, when tested with the non-chromate pretreatment, PreKote. The epoxy control (I) with 2.5 wt% self-healing microcapsules and 2.5 wt% 2-MBT micro particles performed better (rating of 7) than the Epoxy control (I), when tested without a topcoat (rating of 6).

The polythioether were tested without a topcoat (per manufacturer's recommendation), and only with PreKote pretreatment. All polythioether systems failed with similar ratings. Primer 3 in which the inhibitor package was substituted with 2.5 wt% self-healing microcapsules performed slightly better (rating of 7) than the controls (rating of 6). The remainder of the samples performed the same as primer 2 (the uninhibited control). This is somewhat surprising except when considering that primer 1 is recommended to be applied on a chromate pretreatment in commercial applications. This result is consistent with the predominant effect of the pretreatment observed in the epoxy systems.

The above results are consistent with the statement made by ESTCP that "non-chromate primers rely more on the pre-paint surface preparation performance than do chromate primers."[30] Current MIL-PRF-23377 allows qualification of non-chromate primers with chromate conversion coating as a surface pretreatment which poses a technical risk when the non-chromate primer may potentially be combined with a non-chromate pretreatment.

4.3.2 B117 Phase II Test Results

The panels from the B117 Phase II test (Table 9) were analyzed after 2000 hours of salt fog exposure and are shown in Figure 30 to Figure 39. Table 23 shows the ASTM D1654 ratings for the panels.

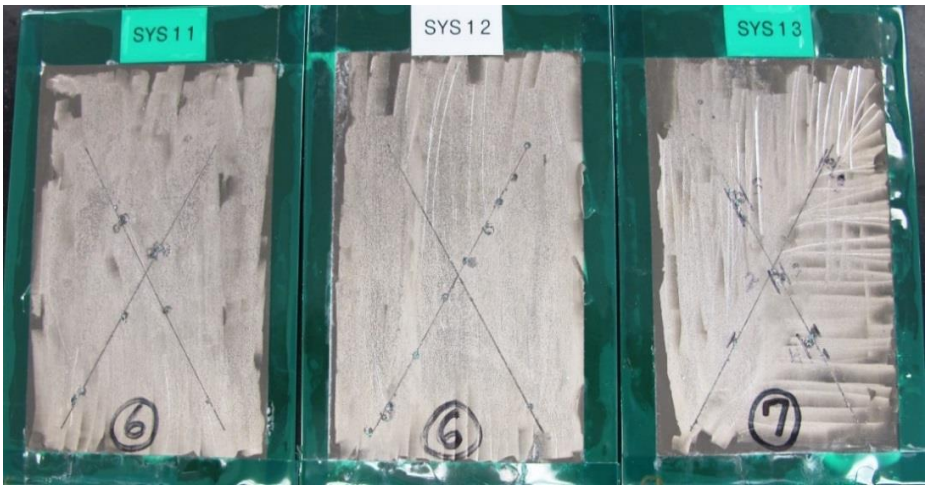

Figure 30. Coating 1 on AA2024-T3 test panels with PreKote pretreatment after 2000 hours of salt fog exposure showing ASTM D1654 ratings with an average of 6.

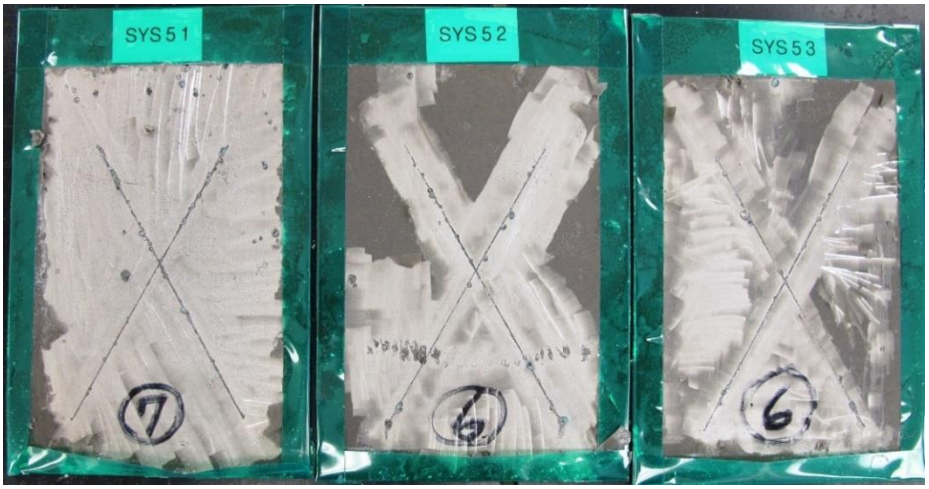

Figure 31. Coating 5 on AA2024-T3 test panels, with PreKote pretreatment, after 2000 hours of salt fog exposure showing ASTM D1654 ratings with an average of 6.

Figure 32. Coating 10 on AA2024-T3 test panels, with Alodine pretreatment, after 2000 hours of salt fog exposure with an average ASTM D1654 rating of 10.

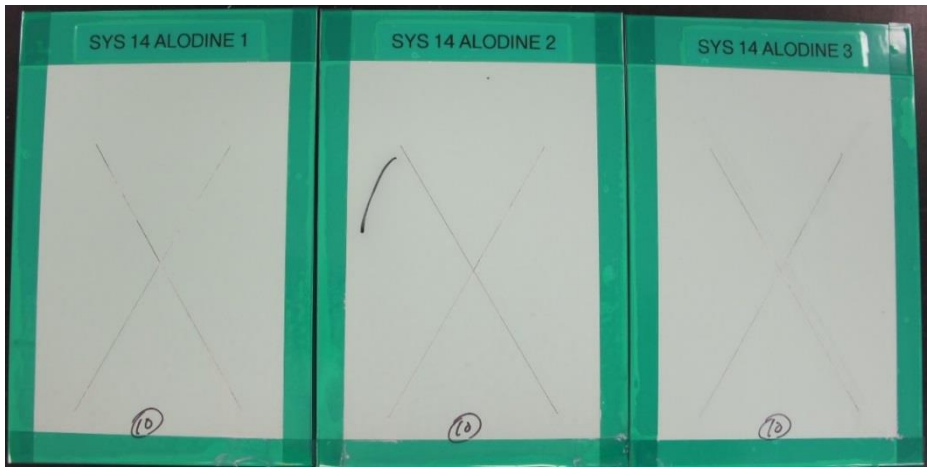

Figure 33. Coating 14 on AA2024-T3 test panels, with Alodine pretreatment, after 2000 hours of salt fog exposure with an average ASTM D1654 rating of 10.

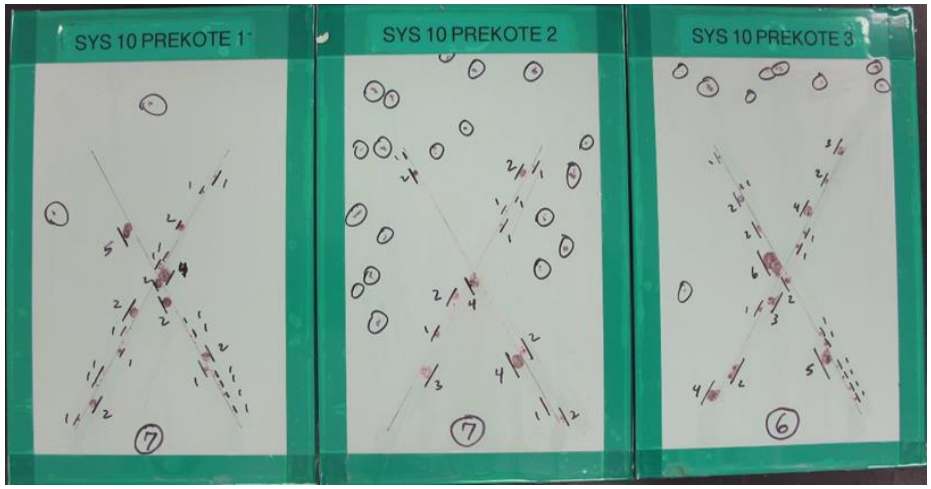

Figure 34. Coating 10 on AA2024-T3 test panels, with PreKote pretreatment, after 2000 hours of salt fog exposure with an average ASTM D1654 rating of 7.

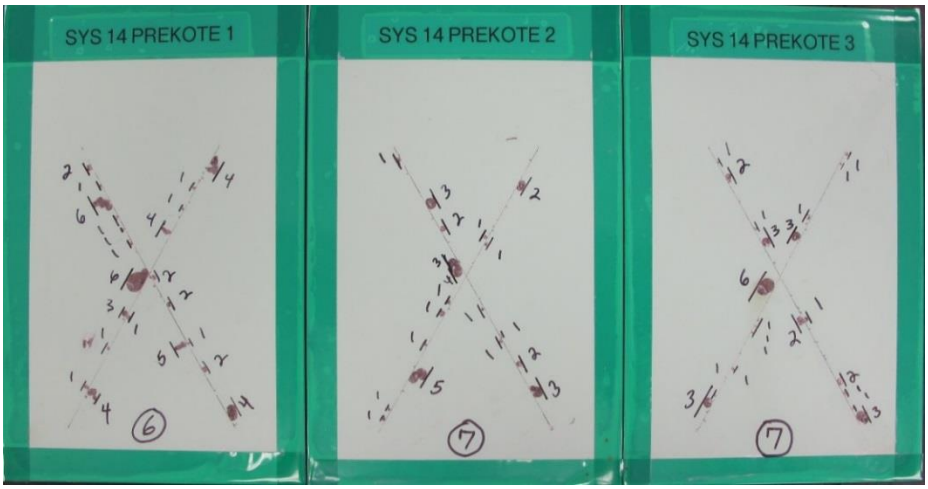

Figure 35. Coating 14 on AA2024-T3 test panels, with PreKote pretreatment, after 2000 hours of salt fog exposure with an average ASTM D1654 rating of 7.

Figure 36. Coating 10T on AA2024-T3 test panels, with Alodine pretreatment and CA9800/F17925 topcoat, after 2000 hours of salt fog exposure with an average ASTM D1654 rating of 10.

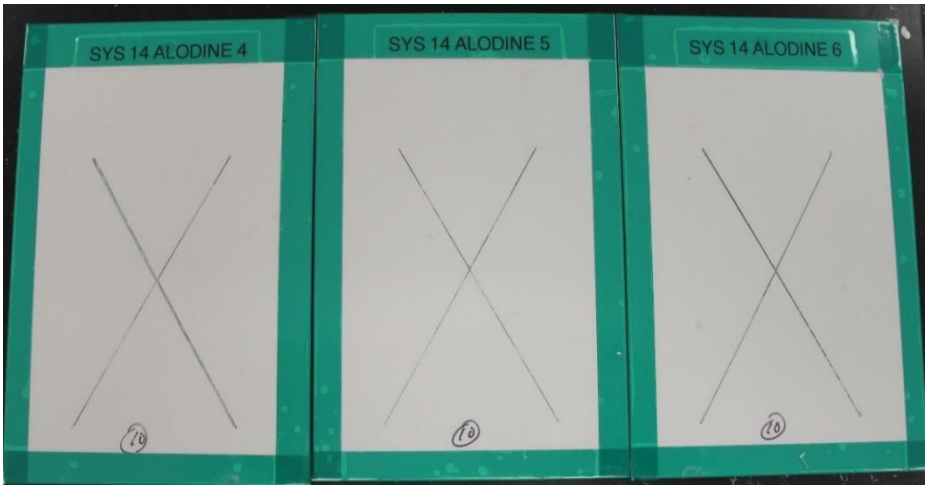

Figure 37. Coating 14T on AA2024-T3 test panels, with Alodine pretreatment and CA9800/F17925 topcoat, after 2000 hours of salt fog exposure with an average ASTM D1654 rating of 10.

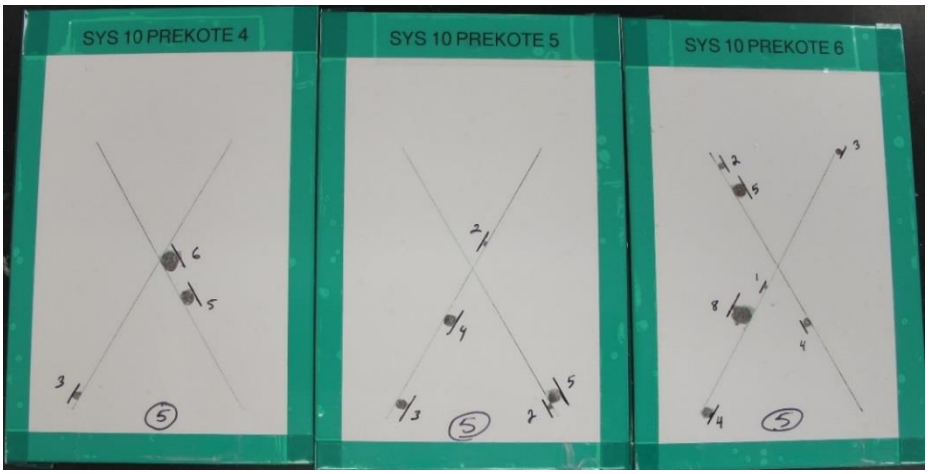

Figure 38. Coating 10T on AA2024-T3 test panels, with PreKote pretreatment and CA9800/F17925 topcoat, after 2000 hours of salt fog exposure with an average ASTM D1654 rating of 5.

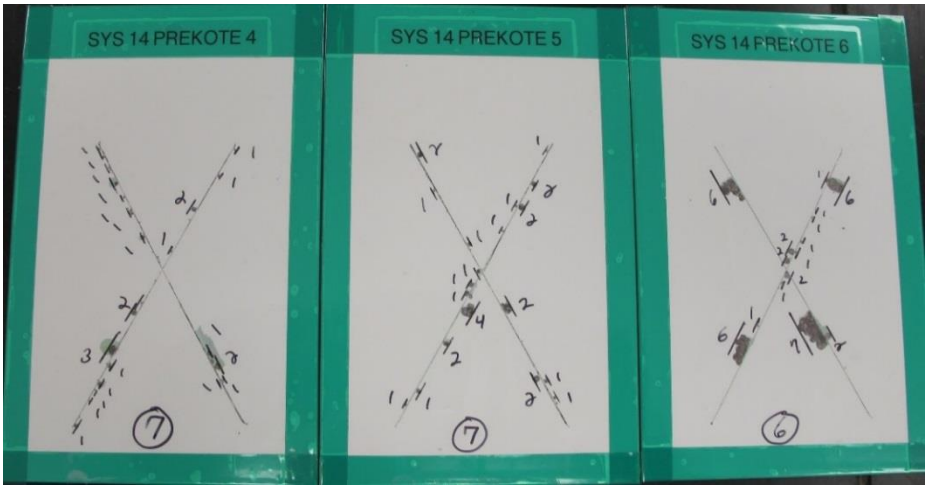

Figure 39. Coating 14T on AA2024-T3 test panels, with PreKote pretreatment and CA9800/F17925 topcoat, after 2000 hours of salt fog exposure with an average ASTM D1654 rating of 7.

The B117 Phase II test was carried out using a smaller group of polythioether primers and a different epoxy primer, but the results confirmed what was observed in the B117 Phase I testing.

The same predominant effect of the pretreatment was observed. There was some slight improvement in some coating testing configurations when the encapsulated inhibitor and the self-healing microcapsules were incorporated into the epoxy primer, but the difference was small. This indicates that the corrosion protection property of a non-chromate coating system is indeed a primer system property, where the metal substrate, pretreatment, primer, and topcoat contribute to the corrosion protection property of the system. Additionally, non-chromate inhibitors which are likely less effective than chromates, rely more on the barrier property of the binder system, as well as requiring more specific water permeability of the resin. The results from these B117 test indicated that replacing the inhibitor package of a primer that meets the MIL-PRF-23377 requirements might be an easy way to test paint compatibility of a new inhibitor package, but it is most likely not the right paint formulation approach to achieve optimized corrosion protection of a non-chromate corrosion inhibitor package.

The B117 test results from this effort were very valuable in guiding the next phase non-chromate epoxy paint formulation. Rather than using a MIL-PRF-23377-qualified epoxy primer, the epoxy paint formulation, for which salt fog test results are shown in Figure 3, will be used as a starting formulation since it has an excellent corrosion protection performance, without a surface pretreatment. Further paint formulation effort will be focused on improving other properties such as flexibility and adhesion, to provide a paint formulation that is ready for field demonstration.

Table 24. ASTM D1654 ratings of B117 Phase II test panels.

Primer Class	Primer ID	Description	Topcoat	Pretreatment	Average Rating
Polythioether	1	Control (inhibited)	None	PreKote	6
	5	With encapsulated inhibitor (2.5 wt%) and healing agent (2.5 wt%)	None	PreKote	6
Epoxy	10	Epoxy Control	None	PreKote	7
			None	Alodine	10
			CA9800/ F17925	PreKote	5
				Alodine	10
	14	Epoxy with encapsulated inhibitor (4.5 wt%) and healing agent (4.5 wt%)	None	PreKote	7
				Alodine	10
			CA9800/ F17925	PreKote	7
				Alodine	10

4.4 Water Resistance

The test panels were removed from the heated DI water solution after four days of immersion in DI water (Figure 40. Two hours after removal, the samples were evaluated and photographed.

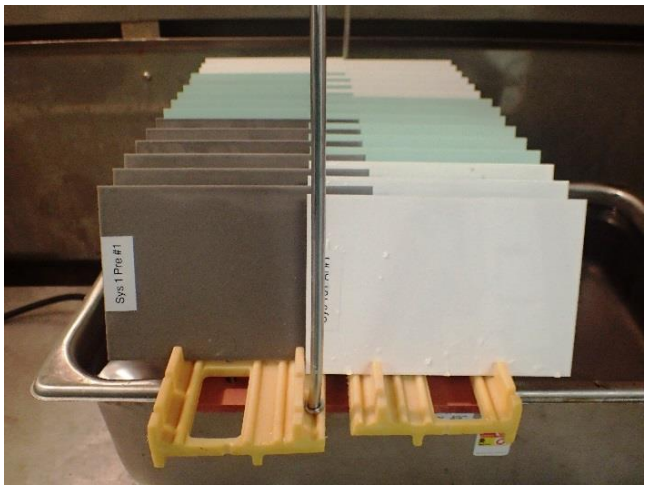

Figure 40. MIL-PRF-23377 water resistance test panels after four days of immersion in DI water.

According to MIL-PRF-23377, the "coatings shall withstand immersion in distilled water maintained at (49 ± 3) °C [(120 ± 5)] °F for 4 days without exhibiting any evidence of wrinkling, blistering, or any other coating deficiency". No coating deficiencies were visible on any of the chrome-free primer systems included in the test (Table 10).

4.5 Filiform Corrosion

The primer coating test panels shown on Table 11 were removed from the humidity cabinet and examined for conformance to the MIL-PRF-23377 filiform corrosion conformance requirement described on section 3.8.2.2. No visible signs of filiform corrosion were evident on any of the panels. All panels were stripped to the bare substrate and evaluated for filiform corrosion under 10X magnification. No evidence of filiform corrosion was observed on any of the panels. Figure 41 shows one of the set of panels that illustrates the results from the filiform corrosion test.

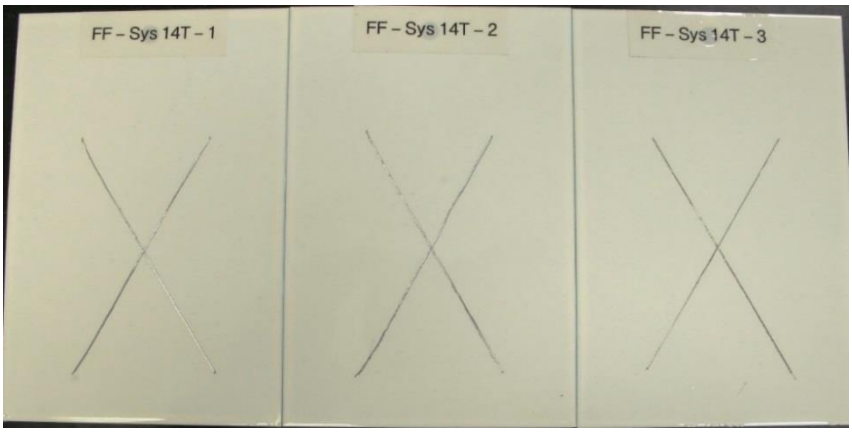

Figure 41. Coating 14T on AA2024-T3 filiform corrosion test panels, with Alodine pretreatment and CA9800/F17925 topcoat, showing no visual evidence of filiform corrosion.

4.6 Fineness of Grind

The chrome-free primers were prepared as shown on Table 25 and immediately spread on a one-path fineness gage, as shown in Figure 42 for Coating 5. The reading of the Heagman scale, done within 10 s of placing the sample on the gage, is given on Table 25 for each of the chrome-free primers. Coatings 10 and 14 met the MIL-PRF-23377 fineness of grind requirement for a value of 5 or greater on the Hegman scale.

Table 25. Hegman Scale values for chrome-free primers.

Primer Class	Primer ID	Description	Hegman Scale Value
Polythioether	1	Polythioether Control	2.5
	5	Polythioether chrome-free primer with encapsulated 2-MBT (2.5 wt%) and self-healing microcapsules (2.5 wt%)	2.5
Epoxy	10	Epoxy Control	5
	14	Epoxy with encapsulated 2-MBT (4.5 wt%) and self-healing microcapsules (4.5 wt%)	5

Figure 42. Coating 5 spread on a one-path fineness gage to determine the Hegman scale value.

4.7 Accelerated Storage Stability

Results from the accelerated storage stability testing for Coating 10, provided by PPG, showed compliance with the MIL-PRF-23377 accelerated storage stability requirement as described on section 3.5.3 of the specification.

4.8 Viscosity

The time in seconds for the unthinned admixed chrome-free primers to flow through a #4 Ford cup was determined immediately after mixing. The average from three measurements is shown on for each primer on Table 26. Primers 10 and 14 met the "40 seconds through a #4 Ford cup maximum viscosity of the un-thinned, admixed primer components" requirement described on section 3.6.3 of the specification.

Table 26. MIL-PRF-23377 viscosity requirement testing results.

Primer Class	Primer ID	Description	Time Through #4 Cup (s)
Polythioether	1	Flexible chrome-free primer (fully inhibited)	88.8
	5	Flexible chrome-free primer (non-inhibited) with 2.5 wt% self-healing microcapsules and 2.5 wt % 2-MBT micro particles	57.2
Epoxy	10	Chrome-free primer (fully inhibited)	13.4
	14	Chrome-free primer (non-inhibited) with 4.5 wt% self-healing microcapsules and 4.5 wt % 2-MBT micro particles	12.4

4.9 Pot Life

The time in seconds for the unthinned admixed chrome-free primers to flow through a #4 Ford cup was determined after four hours of mixing and storage in a closed container. The average from three measurements is shown for each primer on Table 27. Coating 10 was the control and was tested after it was thinned. Coating 14 met the MIL-PRF-23377 pot life requirement while Coatings 1 and 5 did not.

Table 27. MIL-PRF-23377 pot life requirement testing results.

Primer Class	Primer ID	Description	Time Through #4 Cup (s)
Polythioether	1	Flexible chrome-free primer (fully inhibited)	233.8
	5	Flexible chrome-free primer (non-inhibited) with 2.5 wt% self-healing microcapsules and 2.5 wt % 2-MBT micro particles	79.7
Epoxy	10	Chrome-free primer (fully inhibited)	12.6
	14	Chrome-free primer (non-inhibited) with 4.5 wt% self-healing microcapsules and 4.5 wt % 2-MBT micro particles	12.7

4.10 Surface Appearance

All primer coatings did not sag, run, or streak when applied to vertically oriented test panels. The dried films were observed to have a smooth, uniform surface free of grit, seeds, craters, blisters, and other irregularities. No orange peel (wavy appearance) was evident when viewed from six feet away. All the primer coatings met the surface appearance requirement as described on section 3.7.1 of the MIL-PRF-23377 specification.

4.11 Drying Time

Coatings 1 and 5 were tacky 21 hours after application. Coatings 10 and 14 were tack free within 2 hours and dried hard within 4 hours of application thus meeting the MIL-PRF-23377 drying time requirement to be tack free within 5 hours and dry hard within 8 hours of application. Coatings 1 and 5 did not meet this requirement.

4.12 Adhesion

MIL-PRF-23377 adhesion compliance testing was performed on test panels, prepared as described on Table 12.

As described in section 3.4.3 of this document, for adhesion test involved with polythioether primer, panel type E (2024/Prekote) is used in place of the required type C (2024-T3/Alclad/deoxidized) to understand the effect of Prekote on adhesion of polythioether on 2024-T3 substrate.

For adhesion test involved with epoxy primer, panel type F (2024-T3 bare) in place of type C (2024-T3/Alclad/deoxidized) is used to test the adhesion of primer on 2024-T3 without any pretreatment.

The adhesion rating, based on the ASTM Standard D3359 adhesion rating scale shown on Table 13, are given in Table 28.

Table 28. MIL-PRF-23377 Adhesion requirement test results.

Coating System					Average ASTM D3359 Rating	
Primer Class	**Primer ID**	**Topcoat**	**Pretreatment**	**Panel Label**	**Top Coat**	**Substrate**
Polythioether	**1**	None	PreKote	SYS 1 PK 1, 2, 3	N/A	**5A**
	5	None	PreKote	SYS 5 PK 1, 2, 3	N/A	**5A**
Epoxy	**10**	None	Bare	SYS 10 B 1, 2, 3	N/A	**4A**
		CA9800/ F17925	Bare	SYS 10T B 1, 2, 3	**3A**	N/A
	14	None	Bare	SYS 14 B 1, 2, 3	N/A	**4A**
		CA9800/ F17925	Bare	SYS 14T B 1, 2, 3	N/A	**3A**

The MIL-PRF-23377 adhesion requirement is met when the rating is no less than 4A. All the polythioether primer systems (Coatings 1 and 5) met the adhesion requirement with a 5A rating. The epoxy primers (10, 14) met the adhesion requirement with a 4A rating when tested without a topcoat; but they both failed with a 3A rating when tested with a topcoat.

As shown in Figure 44, the topcoated panels failed differently. System 10 failed at the interface between the topcoat and the primer, while system 14 failed between the primer and the substrate. It is possible that the self-healing microcapsules and/or encapsulated 2-MBT improved the adhesion between the topcoat and the coating. A deoxidizing surface cleaning to improve the adhesion property of the epoxy primer will be carried out as part of the follow on effort.

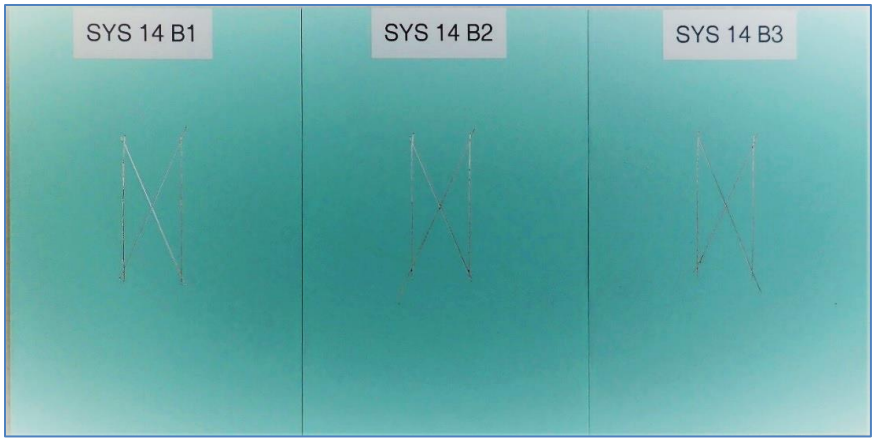

Figure 43. MIL-PRF-23377 Adhesion requirement test results for Coating 14 (without a topcoat).

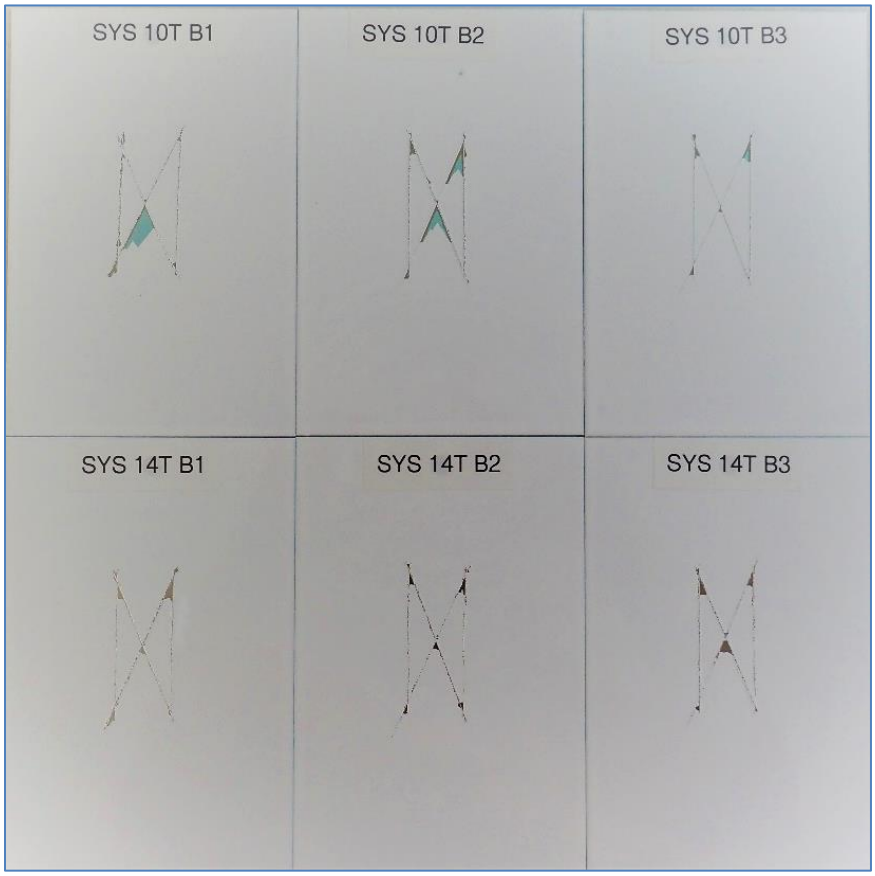

Figure 44. Topcoated panels of primer 10 and 14 tested for adhesion per MIL-PRF-23377.

4.13 Flexibility

The maximum elongation (% area increase) for the chrome-free primer coatings, on anodized aluminum alloy AA2024-0 test panels, included on this testing, is shown on Table 29. As it was expected, both polythioether primers passed the flexibility requirement. Pictures of the

flexibility test panels for epoxy primers 10 and 14 are shown in Figure 45. While the Epoxy Control (Primer 10) met the MIL-PRF-23377 flexibility requirement for "no less than 10% elongation," the epoxy primer containing inhibitor micro particles and self-healing microcapsules (Primer 14) showed poor flexibility. This is likely due to the increased pigment content (9%) in comparison to that of the proprietary control which it is likely to be lower. Further formulation adjustments would be needed to keep the overall pigment/resin ratio well below the critical pigment resin ratio.

Table 29. Maximum elongation (% area increase) and coating thickness for chrome-free primer coatings.

Primer Class	Primer ID	Panel / Pretreatment	Panel Label	Coating Thickness (mils)	Max Elongation (% Area Increase)
Polythioether	**1**	2024-0 anodize	SYS 1 AN 1 SYS 1 AN 2 SYS 1 AN 3	3.2 3.6 3.5	**60** **60** **60**
	5	2024-0 anodize	SYS 5 AN 1 SYS 5 AN 2 SYS 5 AN 3	3.6 3.5 3.6	**60** **60** **60**
Epoxy	**10**	2024-0 anodize	SYS 10 AN 1 SYS 10 AN 2 SYS 10 AN 3	1.4 1.4 1.4	**10** **10** **10**
	14	2024-0 anodize	SYS 14 AN 1 SYS 14 AN 2 SYS 14 AN 3	1.7 1.6 1.6	**0.5** **0.5** **0.5**

Figure 45. Flexibility test panels for coating 10 test panels (top) and coating 14 test panels (bottom).

4.14 Solvent Resistance (Cure)

The solvent resistance test was performed on the coatings described on Table 15 and are shown in Figure 46 after the test was done. All coatings passed the solvent resistance requirement as described in section 3.8.3 of the MIL-PRF-23377 specification.

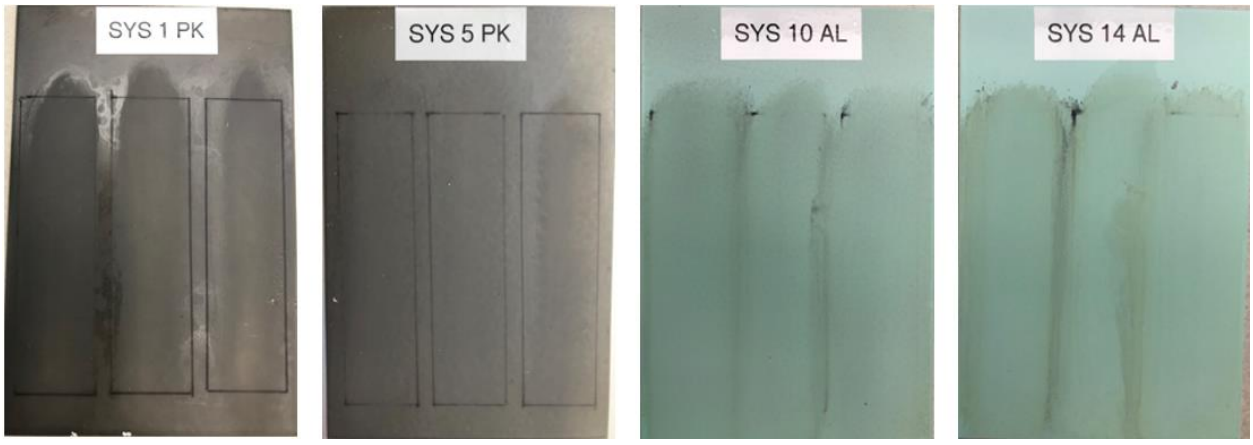

Figure 46. Test panels after MIL-PRF-23377 solvent resistance (cure) testing.

4.15 Fluids Resistance: Lubricating, Hydraulic, Cleaning, and Deicing Fluids

Test panels, prepared as shown on Table 16, were observed visually after remaining in the required fluid for 24 hours and allowed to cool for 4 hours. Each panel was inspected for softening, blistering, loss of adhesion, nor any other coating deficiency. No softening, blistering, loss of adhesion or other issues were visible on any panels as illustrated by the set of panels shown in Figure 48. As shown in Figure 48, some discoloration was observed in some of the coatings but this is acceptable and is not cause for rejection.

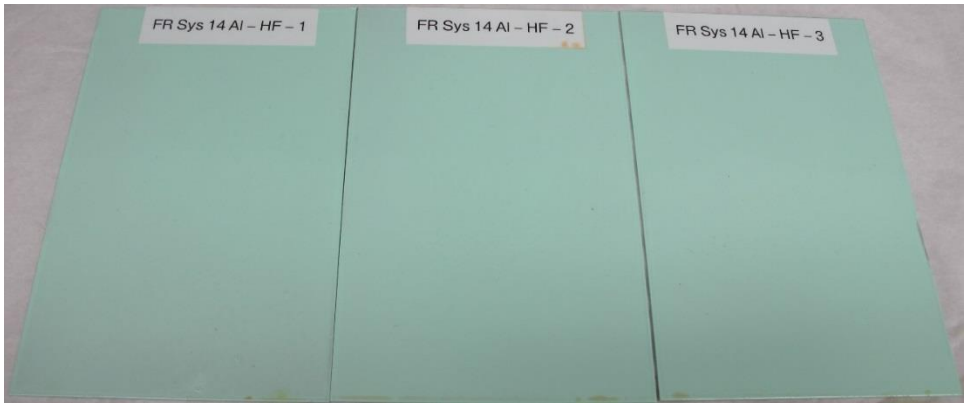

Figure 47. Coating 14 on Alodine pretreated AA2024-T3 panels after MIL-PRF-23377 hydraulic fluid resistance testing.

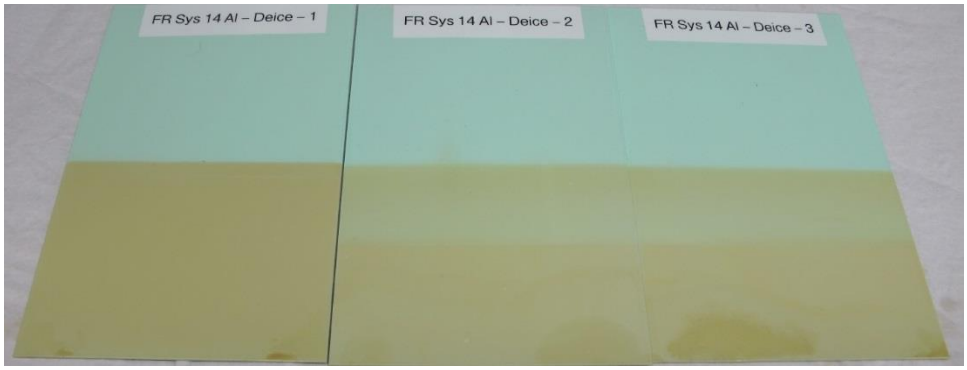

Figure 48. Coating 14 on Alodine-pretreated AA2024-T3 test panels after testing for resistance to deicing fluid.

All the coatings tested met the MIL-PRF-23377 resistance to lubricating and hydraulic fluid requirement. The coatings also met the Weapons System and Platforms Technical Committee directive to provide evidence of resistance to alkaline cleaners and deicing fluids.

4.16 Mixing/Dilution

Coatings 1, 5, 10, and 14 appeared to blend homogeneously when mixed by a paint shaker in the volume mixing ratio, specified by the manufacturer, and did not separate into visually distinct layers within one hour of mixing thus meeting the MIL-PRF-23377 mixing and dilution requirement as described in section 3.9.1 of the specification.

4.17 Application

As shown on Figure 49, coatings 1, 5, 10, and 14 were capable of being applied by conventional, airless, high volume/low pressure (HVLP) that yielded a uniform film with no runs or sags with an average dry-film thickness of 2 mil (Table 9) which is higher than the 0.6 to 0.9 mil given in the specification.

Figure 49. HVLP primer coating application.

4.18 Health Hazard Assessment

The health hazard assessment for the new encapsulated 2-MBT formulation was performed by William S. Eck, Ph.D. at the U.S. Army Public Health Center (APHC) Health Effects Division. It was recommended that measures should be taken to address some of the data gaps outlined in the report via experimental work, although none of these factors appears critical to acceptance of this formulation. Notably, there is a question regarding the acute oral toxicity of 2-MBT in rats, with the value of 100 mg/kg being reported, but unverified. Little publicly documented experimental information is available for PTT. This shortfall could be addressed as time and resources permit, but is not critical to the current project. There are no significant information shortfalls for the remaining compounds in the formulation. The full report in included as Appendix A.

4.19 Strippability

MIL-PRF-23377 strippability requirement testing was performed on the test panels described in Table 17. All the panels tested using method A met the MIL-PRF-23377 strippability requirement as described on section 4.5.13 of the specification. As Figure 50 shows for Coating 14, a minimum of 90 percent of the coating was stripped by one of the methods (Method A). Figure 51 shows the results obtained using Method B on the same coating where none of the coating was removed. All the panels tested using Method B failed to meet the MIL-PRF-23377 strippability requirement as described on section 4.5.13 of the specification.

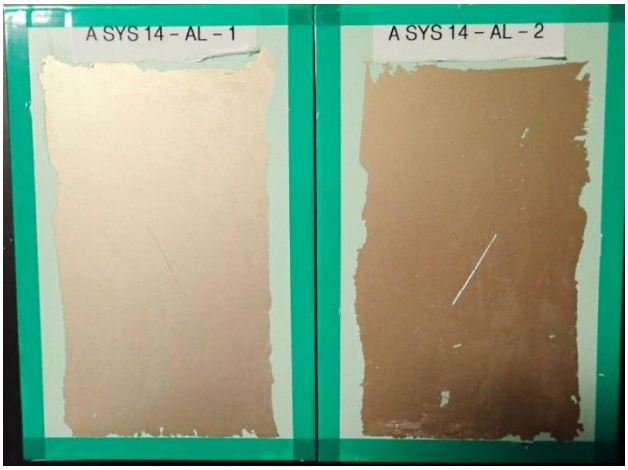

Figure 50. MIL-PRF-23377 strippability requirement test results for Coating 14 using method A.

Figure 51. MIL-PRF-23377 strippability requirement test results for Coating 14 using method B.

Table 30 shows an overview of the MIL-PRF-23377 compliance testing results for the chrome-free primer formulations included on this project (Table 3). Compliance with the MIL-PRF-23377 requirement is entered as Y (yes), N (no) or N/A (not applicable, i.e. not tested).

In summary, the MIL-PRF-23377 was used to evaluate the material compatibilities of the encapsulated inhibitor/healing agent and to facilitate the optimization of the paint formulation. To address the potential risk associated with combining Cr(VI)-free primers with Cr(VI)-free pretreatments, that are qualified separately, some additional tests with a non-chromate pretreatment, such as PreKote, were performed, that were beyond the scope of the direction given by SERDP, but that otherwise followed the procedures of the MIL-PRF-23377. Two types of primers were selected for testing in this work: a solvent based epoxy and a polythioether primer. The polythioether primer was included to address the need for a flexible chrome-free primer to mitigate the degradation of aircraft outer mold line (OML) materials.

Overall, the encapsulated inhibitors/healing agent showed excellent materials compatibility and performed equal or better than the control. The only exception was the flexibility in the epoxy system, where the epoxy containing inhibitor and healing agents showed poor flexibility. This is likely due to the increased pigment content in comparison to that of the control. Further formulation adjustments are needed to keep the overall pigment/resin ratio well below the critical pigment resin ratio. The epoxy primers passed the B117 test requirements when tested with chromate pretreatment but failed when tested with PreKote non-chromate pretreatment, in both Phase I and Phase II testing. These tests results will be used to facilitate the formulation choice for the next epoxy primer optimization step prior to the field demonstration.

Table 30. Summary of MIL-PRF-23377 compliance testing results

MIL-PRF-23377 Requirement	Test	Coating Systems Test	Test Results			
			1	5	10	14
Physical properties – Paint before and after mixing	Fineness of grind	Primer Paint	N	N	Y	Y
	Accelerated storage stability	Primer Paint (10 only)	N/A	N/A	Y	N/A
	Viscosity	Primer Paint	N	N	Y	Y
	Pot life	Primer Paint	N	N	Y	Y
Physical properties – film	Surface appearance	Primer	Y	Y	Y	Y
	Drying time	Primer	N	N	Y	Y
	Adhesion	Primer: 1, 5 Primer and Topcoated: 10, 14	Y	Y	Y (primer) N (topcoated)	Y (primer) N (topcoated)
	Flexibility	Primer	Y	Y	Y	N
Resistance	Water	Primer: 1, 5 Primer and Topcoated: 10, 14	Y	Y	Y	Y
	Salt-spray corrosion	Primer: 1, 5 Primer and Topcoated: 10, 14	N	N	Y	Y
	Filiform corrosion	Primer only: 1, 5 Topcoated: 10, 14	Y	Y	Y	Y
	Solvent (cure)	Primer	Y	Y	Y	Y
	Fluids: Lubricating oil hydraulic fluid	Primer	Y	Y	Y	Y
Working Properties	Mixing/dilution	Primer Paint	Y	Y	Y	Y
	Application	Primer Paint	Y	Y	Y	Y
Toxicity	Health Hazard Assessment	Primer Paint:	Y	Y	Y	Y
Strippability	Strippability	Primer	Y	Y	Y	Y

5. CONCLUSIONS AND IMPLICATIONS FOR FUTURE RESEARCH

This proposed Limited Scope study was performed to meet specific direction from the SERDP Weapons Systems and Platforms Technical Committee to achieve the following objectives:

(1) Scale-up of materials that can meet MIL-PRF-23377 (solvent-based primer).
(2) Provide evidence of resistance to aircraft alkaline cleaners and deicing fluids.
(3) Provide formulation for initial ecological and toxicity screening.
(4) Submit an interim report that will provide the basis for a future ESTCP demonstration effort.

The encapsulation process was successfully scaled-up to 2.0 kg scale through collaboration with Autonomic Materials Inc. (AMI) to demonstrate producibility.

Encapsulated corrosion inhibitor, 2-MBT, and self-healing microcapsules were incorporated into paint formulations recommended by PPG; paint formulation compatibilities of the chromate

alternative materials were demonstrated using MIL-PRF-23377 testing as a guidance. Additional fluid resistance testing was performed to show resistance to aircraft alkaline cleaners and deicing fluids. Overall, the encapsulated inhibitors/healing agents showed excellent materials compatibility. The only exception was the flexibility at high pigment loading, which will be addressed with a further paint formulation effort. Epoxy primers passed B117 when tested with chromate pretreatment, but failed when tested with PreKote non-chromate pretreatment. These tests result will facilitate the formulation choice for the next epoxy primer optimization step before demonstration.

The initial ecological and toxicity screening, performed by the APHC, concluded that most of the proposed components are of low to moderate toxicity and are not a significant concern.

This report is submitted to provide the basis for the follow-on ESTCP demonstration/validation effort.

LITERATURE CITED

[1] MIL-PRF-23377K, Performance Specification: Primer Coatings: Epoxy, High-Solids (07-Jun-2012).

[2] https://www.serdp-estcp.org/Featured-Initiatives/Green-Manufacturing-and-Maintenance/Hexavalent-Chromium (accessed September 7. 2018).

[3] International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risk of chemicals to man: some inorganic and organometallic compounds (1973). http://monographs.iarc.fr/ENG/Monographs/vol1- 42/mono2.pdf (accessed December 13, 2018).

[4] Occupational Safety & Health Administration [OSHA], Chromium (VI) standard, 29 CFR 1910.1026.

[5] DFARS Minimizing the Use of Hexavalent Chromium, Federal Register /Vol. 76, No. 87 /Thursday, May 5, p 25569 (2011).

[6] Cadmium and Hexavalent Chromium Alternatives 5-Year Strategy and Roadmap, Contract # W9128F-12-D-0041, May 25, 2016, https://www.google.com/search?q=++cadmium+and+hexavalent+chromii,+5-year (accessed February 20, 2019).

[7] Julia Russell, Status of NC Prime Demonstration & Transition, Presented at ASWTS Defense 2014, 20 November 2014.

[8] Chromate Primer Alternatives, ASETSDefense Workshop 2016, http://www.asetsdefense.org/ChromeFreePrimer.aspx (accessed September 7, 2018).

[9] J. Russell, Comprehensive Evaluation and Transition of Non-Chromate Primers within DoD (WP-201131), ASETS Defense 2012.

[10] Peter Zarras and Cindy Webber, Validation/Demonstration of Anti-Corrosion Inhibitor Primer Formulations as Replacements for Hexavalent Chromium (Cr(VI) Military Primer Coatings, ESTCP Joint Technical Report, Weapons Systems and Platforms Project WP-200904, March

2015. https://www.serdp-estcp.org/Program-Areas/Weapons-Systems-and-Platforms/Surface-Engineering-and-Structural-Materials/Coatings/WP-200527 (accessed September7, 2018).

[11] J. W. Buhrow, W. Li, S. J. Jolley, L. M. Calle, B. P. Pearman, and X. Zhang, "Testing and Evaluation of Multifunctional Smart Coatings," 2015 Department of Defense – Allied Nations Technical Corrosion Conference, Pittsburgh, PA, November 15-19, 2015.

[12] Rudolph G. Buchheit, Critical Factors for the Transition from Chromate t Chromate-Free Corrosion Protection, SERDP Final Report PP-1119 (2005).

[13] J. Sinko, Challenges of chromate inhibitor pigments replacement in organic coatings, Progress in Organic Coatings 42 (2001) 267-282.

[14] M. Kendig and C. Yan, Critical Concentrations for Selected Oxygen Reduction Reaction Inhibitors, Journal of the Electrochemical Society 151 (12) B679-B682 (2004).

[15] C. Matzdorf, Using Corrosion Design Models to Accelerate the Transition of Alternatives, ASETSDefense 2012: Sustainable Surface Engineering for Aerospace and Defense Workshop, August 27-30, 2012, San Diego, CA.

[16] K. E. Gulbrandsen, "Bridging the Valley of Death: The Rhetoric of Technology Transfer," (2009). Graduate Theses and Dissertations. 10740. https://lib.dr.iastate.edu/etd/10740, (accessed September 10, 2018).

[17] S. Doheny-Farina, "Rhetoric, innovation, technology: Case studies of technical communication in technology transfers. Cambridge: MIT Press, (1992).

[18] Coppola, N. Communicating green innovation technology: Transfer in a university business-government consortium. *Comparative Technology Transfer and Society, 5*, 233-252, (2007).

[19] ASTM Standard B117-18, "Standard Practice for Operating Salt Spray (Fog) Apparatus," ASTM International, West Conshohocken, PA, 2018.

[20] S. R. White, N. R. Sottos, P. H. Geubelle, J. S. Moore, M. R. Kessler, S. R. Sriram, E. N. Brown and S. Viswanathan, Autonomic healing of polymer composites, Nature, 409, 2001.

[21] G.O. Wilson, "Life Extension In Protective Coatings Via Self-Healing Technology," https://repository.tudelft.nl/islandora/object/uuid:b86b8489-7609-401d-8a9a-23b3ad0aa890/datastream/OBJ/download (accessed February 22, 2019).

[22] Autonomic Materials™, Technical Data Sheet, Amparmor™2000, https://www.autonomicmaterials.com/Portals/0/Assets/PDF/AMPARMOR-2000-TDS.pdf, (accessed February, 20, 2019).

[23] R. Botet, The "ouzo effect", "Recent Developments and Application to Therapeutic Drug Carrying," Journal of Physics: Conference Series 352, 012047, 2012.

[24] L.M. Calle, and W. Li, "Coating and methods for corrosion detection and/or reduction," US Patent 7,790,225.

[25] W.Li, J.W. Buhrow, S.T. Jolley, and L.M. Calle, "pH-Sensitive micro particles with matrix-dispersed active agent," US Patent 8,859,288.

[26] L.M. Calle, W. Li, J.W. Buhrow, S.A. Perusich, S.T. Jolley, T.L. Gibson, and M.K. Williams, "Elongated microcapsules and their formation," US Patent 9,108,178.

[27] L.M. Calle, W. Li, J.W. Buhrow, and S.T. Jolley, "Hydrophilic-core microcapsules and their formation," US Patent 9,227,221.

[28] L.M. Calle, W. Li, J.W. Buhrow, and S.T. Jolley, "Hydrophobic-core microcapsules and their formation," US Patent 9,233,394.

[29] J. Zhang, W. Li, and L.M. Calle, "Inorganic delivery systems and coatings for multi-stimuli controlled-release of corrosion protective agents and methods for their preparation," Provisional Patent 2015.

[30] https://www.serdp-estcp.org/Funding-Opportunities/ESTCP-Solicitations/Past-solicitation-pages/Environmental-Technologies-Solicitation-18/Outside-DoD-Federal-Proposal-Instructions/FY18-ESTCP-Federal-Outside-DoD-WP-Topic-B6-Hexavalent-Chromium-Altneratives

[31] ASTM D1210, "Standard Test Method for Fineness of Dispersion of Pigment-Vehicle Systems by Hegman-Type Gage," ASTM International, West Conshohocken, PA, 2005 (R 2014).

[32] ASTM D1200, "Standard Test Method for Viscosity by Ford Viscosity Cup, ASTM International, West Conshohocken, PA, 2010 (R 2018).

[33] ASTM D5895, "Standard Test Methods for Evaluating Drying or Curing During Film Formation of Organic Coatings Using Mechanical Recorders," ASTM International, West Conshohocken, PA, 2013.

[34] ASTM D3359, "Standard Test Methods for Rating Adhesion by Tape Test," ASTM International, West Conshohocken, PA, 2017.

[35] ASTM D6905, "Standard Test Method for Impact Flexibility of Organic Coatings," ASTM International, West Conshohocken, PA, 2003 (R 2012).

[36] ASTM D2803, "Standard Guide for Testing Filiform Corrosion Resistance of Organic Coatings on Metal," ASTM International, West Conshohocken, PA, 2009 (R 2015).

[37] ASTM D5402, "Standard Practice for Assessing the Solvent Resistance of Organic Coatings Using Solvent Rubs," ASTM International, West Conshohocken, PA, 2015.

[38] MIL-PRF-23699G, Performance Specification, Lubricating Oil, Aircraft Turbine Engine, Synthetic Base, NATO Code Numbers: O-152, O-154, O-156, and O-167 (13-MAR-2014).

[39] MIL-PRF-83282D, Performance Specification: Hydraulic Fluid, Fire Resistant, Synthetic Hydrocarbon Base, NATO Code Number H-537 (30 SEP 1997).

[40] TT-R-2918, Federal Specification: Remover, Paint, No Hazardous Air Pollutants (HAPs), Revised 05-Jun-2006.

[41] MIL-R-81294, Military Specification: Remover, Paint, Epoxy, Polysulfide, and Polyurethane Systems, Amended 15-December 1999.

[42] ASTM Standard D 1654, "Standard Test Method for Evaluation of Painted or Coated Specimens Subjected to Corrosive Environments," ASTM International, West Conshohocken, PA, 2003.

APPENDIX A

Toxicology Report No. S.0058900.3-18, May 2019
Toxicology Directorate

Toxicology Assessment for Department of Defense Strategic Environmental Research and Development Program (SERDP) Project WP18-1531: Development of Controlled-Release Corrosion Inhibitors and Healing Agents as Alternatives to Hexavalent Chromium, March 2018–April 2019

Prepared by William S. Eck, Ph.D.,
Health Effects Division

Approved for public release; distribution unlimited.

General Medical: 500A, Public Health Data

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
04/15/2019	Technical Report	March 2018-April 2019

4. TITLE AND SUBTITLE
Toxicology Assessment for Department of Defense Strategic Environmental Research and Development Program (SERDP) Project WP18-1531: Development of Controlled-Release Corrosion Inhibitors and Healing Agents as Alternatives to Hexavalent Chromium

5a. CONTRACT NUMBER

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
William S. Eck, Ph.D.

5d. PROJECT NUMBER
WP18-1531

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Toxicology Directorate
Army Public Health Center (APHC)
Aberdeen Proving Ground, MD 21010

8. PERFORMING ORGANIZATION REPORT NUMBER
S.0058900.3-18

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Department of Defense
Strategic Environmental Research and Development Program (SERDP)

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)
WP18-1531

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution unlimited.

13. SUPPLEMENTARY NOTES
None

14. ABSTRACT
Corrosion control is a significant problem for military equipment. Many surface treatment materials currently in use on items of military or aerospace materiel contain chromium(VI) as a component, a source of significant human health and environmental hazard. The formulation under evaluation contains no chromium. Most of the proposed components are of low to moderate toxicity and are not a significant concern. Two of the formulation components are associated with some cancer hazard–2-mercaptobenzothiazole and formaldehyde, but both find widespread use in industry and additional investigation is not required for this project.

15. SUBJECT TERMS
chromium, 2-mercaptobenzothiazole, formaldehyde, corrosion protection.

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			William S. Eck, Ph.D.
U	U	U	UU	51	19b. TELEPHONE NUMBER *(Include area code)*: 410-436-3980

ACKNOWLEDGEMENT

The author would like to acknowledge the support and encouragement provided to this effort by Dr. Robin Nissan, Program Manager, Weapons Systems and Platforms, Strategic Environmental Research and Development Program (SERDP).

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May 2019

1 Summary

1.1 Overview

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 alternative substances before they are fielded. Continuous assessments begun early in the research, development, testing and evaluation (RDT&E) process can save significant time and effort not only during RDT&E but over the life cycle of the items developed, as well. Residues of pyrotechnics, propellants, explosives and incendiaries used in mission-essential activities have been found in soil, air, surface, and groundwater samples. Remediation of contaminated areas has cost the Department of Defense (DOD) millions of dollars and can interfere with training activities.

1.2 Purpose

This report is a toxicological evaluation of a new formulation for a project whose objective is to demonstrate and validate controlled-release corrosion inhibitors as alternatives to the hexavalent chromium [Cr(VI)] (chromate)-containing primers currently used on a variety of weapon systems. The overall project also intends to address accelerated aging protocols that can simulate more accurately, in the laboratory, degradation mechanisms that occur during actual service conditions and that can shorten decision times. This project addresses the DOD goal to reduce the use of Cr(VI) at DOD maintenance depots by 90% or more by the end of Fiscal Year 2020 and to comply with a memorandum calling for the reduction of Cr(VI)-containing primers across the DOD. Alternatives to Cr(VI) primers are important to reduce both hazardous waste and detrimental effects on readiness and the environment, as well as to ensure the safety of workers applying or removing the primers.

1.3 Conclusions

A cancer hazard is associated with 2-mercaptobenzothiazole (2-MBT) and formaldehyde. While there are data gaps for some of the other compounds in this formulation, most of the hazard is derived from typical occupational concerns, such as dermal and ocular irritation, that are normally addressed via personal protective equipment (PPE). For some compounds, there are additional issues, but there are factors in mitigation. For example, while 2-MBT is classified as highly toxic, it is widely used in industrial rubber products. Although there is no epidemiological evidence of serious, 2-MBT-related health issues in humans, workers exposed to 2-MBT have been found to be at increased risk of bladder cancer. Formaldehyde represents a potential concern, as it is a likely human carcinogen. It also poses a hazard for inhalation, oral, and

dermal exposures in addition to moderate dermal, ocular, and neurological effects. The remaining compounds in the alternative formulation are of low to moderate toxicity and not thought to be a serious exposure concern.

1.4 Recommendations

Measures should be taken to address some of the data gaps outlined in this report via experimental work, although none of these factors appears critical to acceptance of this formulation. Notably, there is a question regarding the acute oral toxicity of 2-MBT in rats, with the value of 100 mg/kg being reported but unverified. Little publicly documented experimental information is available for pentaerythrytol tetrakis(3-mercaptopropionate) (PTT). This shortfall could be addressed as time and resources permit but is not critical to the current project. There are no significant information shortfalls for the remaining compounds in the formulation.

2 References

See Appendix A for list of the references cited in this report.

3 Authority

Funding for this work was provided under Military Interdepartmental Purchase Request No. W74RDV80244410. This Toxicology Assessment addresses, in part, the environment, safety and occupational health (ESOH) requirements outlined in the following—

- Department of Defense Instruction 4715.1E, Environment, Safety, and Occupational Health (ESOH), 2005; Change 1, 2018;
- Army Regulation (AR) 200–1, Environmental Protection and Enhancement, 2007;
- AR 40–5, Preventive Medicine, 2007;
- AR 70–1, Army Acquisition Policy, 2018; and
- Army Environmental Requirement and Technology Assessment (AERTA) Requirement PP-2-02-06, Toxic Metal Reduction in Surface Finishing of Army Weapons Systems.

The Sponsor is the DOD Strategic Environmental Research and Development Program (SERDP). The Principal Investigator is Dr. Luz Marina Calle, NASA John F. Kennedy Space Center.

4 Background

Current regulations require assessment of human health and environmental effects arising from exposure to substances in soil, surface water, and groundwater. If 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 to avoid unnecessary costs, conserve physical resources, and sustain the health of U.S. Forces and others potentially exposed.

In an effort to support this preventive approach, the U.S. Army Public Health Center (APHC) has been tasked with creating a phased process to identify ESOH effects impacting readiness, training, and development costs. This report represents the status of information available for this work unit as of the date of publication.

5 Statement of Problem

Cr(VI) is a component of many surface treatment materials currently used on items of military and aerospace materiel. While Cr(VI) has been demonstrated to provide excellent performance, it is a significant human health and environmental hazard. In 2009, the DOD issued a memorandum calling for reduction in use of Cr(VI) across the Department. This project will develop a coating that not only provides a high level of corrosion protection but also employs encapsulation technology to facilitate correction of defects that develop in coated surfaces.

6 Methods

In order to determine the human health and environmental impact of compounds employed in these alternative formulations, it is necessary to identify each compound correctly 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 (CAS RN) (Table 1). While all compounds do not necessarily have a single CAS RN, the CAS RN is an unambiguous means of accessing information about chemical substances. The CAS RN is readily used as a keyword for searching online databases and is often cross-referenced with both systematic and trivial (i.e., “common” or non-systematic) names for chemical substances. In some cases, synonyms and trade names are also used to identify structures.

Table 1. Formulation Components and Predicted Products

Chemical Substance	CAS Number
2-Mercaptobenzothiazole	149-30-4
Melamine	108-78-1
Formaldehyde	30525-89-4
Pentaerythritol tetrakis(3-mercaptopropionate)	7575-23-7
Sodium dodecyl sulfate	151-21-3

Chemical Substance	CAS Number
Gum arabic	9000-01-5
Tetrahydrofuran	109-99-9
p-Toluenesulfonic acid	104-15-4

The properties necessary to assess fate and transport in the environment (FTE) include—

- Molecular weight (MW).
- Boiling point (bp).
- Octanol-water partition coefficient (log K_{OW}).
- Organic carbon partition coefficient (log K_{OC}).
- Water solubility.
- Henry's Law constant (K_H).
- Vapor pressure (vp).

Basic physical and chemical properties are usually determined by consulting tertiary sources when such information is available.

Toxicological information needed to estimate potential human health risks includes reported toxicity effects of oral, inhalation, dermal, and ocular exposures; potential for developmental or reproductive toxicity, neurotoxicity, genotoxicity, and carcinogenicity; and mode(s) and mechanisms of toxicity. Toxicological information is derived directly from primary sources whenever possible.

Sources used in this search included *The Merck Index* (O'Neil 2006, Budavari 1996); the U.S. National Library of Medicine's Toxicology Data Network (TOXNET®), providing access to information from the National Institutes of Health (NIH) and the U.S. Environmental Protection Agency (EPA); the U.S. Department of Health and Human Services' Agency for Toxic Substances and Disease Registry (ATSDR); the EPA ECOTOXicology Database System (ECOTOX); the National Center for Biotechnology Information's PubChem® database, and the Defense Technical Information Center (DTIC®). Additional sources may include publications

from the U.S. National Institute for Occupational Safety and Health (NIOSH), the World Health Organization (WHO), and the International Agency for Research on Cancer (IARC).

Primary references are identified and retrieved via PubMed® and the ProQuest® Databases. TOXNET provides links to a suite of individual databases including ChemIDPlus® (chemical structures, registration numbers, and links to other sites providing physical chemical properties of the compound), the Hazardous Substances Data Bank (HSDB®), TOXLINE® (references to literature on biochemical, pharmacological, physiological and toxicological effects of drugs and other chemicals), the Developmental and Reproductive Toxicology (DART) database, the Comparative Toxicogenomics Database (CTD), the Integrated Risk Information System (IRIS), and the Animal Testing Alternatives (ALTBIB) database, as well as several others, including the archived databases for the Chemical Carcinogenesis Research Information System (CCRIS), the Carcinogenic Potency Database (CPDB), and GENE-TOX genetic toxicity database. Commercial suppliers may provide results of in-house research that do not appear in the open literature.

Persistence, bioaccumulation, human health toxicity, and ecotoxicity were assigned to general categories of risk (i.e., low, moderate, or high) based on criteria modified from Howe et al. (2006). Table 2 describes the criteria used in the categorization; the relative proportions of each substance were also factored into the final assessment. Appendix B provides the Globally Harmonized System (GHS) classifications (Occupational Safety and Health Administration (OSHA) 2012) for many of these compounds.

Table 2. Categorization Criteria used in the Development of Environmental Safety and Occupational Health Severity[1]

	Low	Moderate	High
PERSISTENCE	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:

LC_{50} = concentration expected to result in 50% lethality to a population of test animals
LOAEL = lowest-observed adverse effect level
mg/kg-d = milligrams per kilogram per day
mg/L = milligrams per liter
µg/L = micrograms per liter
Note:
[1] Modified from Howe et al. 2006

7 Results

7.1 Physical and Chemical Properties

Table 3 summarizes the physical and chemical properties of the alternative compounds. "ND" indicates no data were found, and "n/a" indicates the property named is not applicable to the substance being described. For example, if the compound is a nonvolatile solid or an inorganic salt, the vp, K_{OW}, K_{OC}, and K_H are typically negligible.

Table 3. Physical Properties

Compound	Molar Mass (g/mol)	Melting Point (ºC)	Boiling Point (ºC)	Aqueous solubility (mg/L) @ 25ºC	log K_{ow}	log K_{oc}	Henry's Law Constant (atm-m^3/mol) @ 25ºC	Vapor Pressure mmHg @ 25°C
2-Mercaptobenzothiazole	167.244[a]	180.2–181.7[a]	Dec[a]	51[a]	2.41[a]	2.51–3.55[a]	4.1E-11[a]	<1.9E-06[a]
Melamine	126.12[b]	354[b] (exp)	Sublimes[b]	3240[b] (exp)	-1.37[b] (exp)	5[3] (est)	1.84E-14[2] (est)	3.59E-10 at 20ºC[b]
Formaldehyde	30.026[c]	-92[c]	-19.1[c]	Miscible[c]	0.35[c]	1.567[d]	3.27E-07[d]	3.890[c]
Pentaerythrytol tetrakis(3-mercaptopropionate)	488.64[e]	-40.09[f]	275 at 1 mmHg[f]	5.224[g]	3.03[f]	2.227[g]	3.62E-17[g]	4.8E-11[g]
Sodium dodecyl sulfate	288.378[h]	205.5[h]	Dec	1.5E+05[h]	1.6[h]	3.50[h]	1.8E-07[i]	4.7E-13[h]
Gum arabic	≥240,000[J]	ND	ND	Highly soluble[J]	ND	ND	ND	Negligible[J]
Tetrahydrofuran	72.107[k]	-108.44[k]	65.0[k]	Miscible[l]	0.46[k]	1.31[m]	7.05E-05[k]	132[l]
p-Toluenesulfonic acid	172.019[n]	106[o]	140[o]	Very soluble[o]	0.9[n]	0.582[m]	2.78E-09[p]	2.7E-06[p]

Legend:
ºC = degrees Celsius
Dec = decomposes
g/mol = grams per mol
mmHg = millimeters Mercury
ND = No Data

Key:
a = PubChem 2019a
b = PubChem 2019b
c = PubChem 2019c
d = ATSDR 1999
e = ChemIDPlus 2019

f = Sigma-Aldrich 2014
g = EPI Suite 4.11 prediction
h = PubChem 2019e
i. = HSDB 2000
j = HSDB 2002
k. = PubChem 2019
l. = NIOSH 2018
m. = calculated from mean K_{oc} value
n. = PubChem 2019g
o. = Budavari 1996
p. = HSDB 1995

7.2 Compound Summaries

Table 4 summarizes the mammalian toxicity data. Tables 5 and 6 present assessments of human health and environmental toxicity, respectively, for each formula component. Each characterization is generally based on the criteria in Table 2. The final risk characterization also incorporates an 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.

Table 4. Toxicity Data

Compound	Acute Oral LD_{50} (mg/kg)	Chronic Oral LOAEL (mg/kg-d)	Inhalation LC_{50} (g/m^3-h)	Dermal	Ocular	Genotoxicity	Carcinogenicity
2-Mercaptobenzo-thiazole	100[a]	71.3[b]	7.5E-03[b]	Sensitizer[q]	Irritant[a]	Negative[a]	Possible[a]
Melamine	3296[c]	112.5[d]	1500[b]	Negative[a]	Mild irritant[e]	Negative[f]	Positive in male rats[f]
Formaldehyde	800[g]	ND	1.07[g]	Irritant, likely sensitizer[h]	Irritant[h]	Positive	Probable human carcinogen[g]
Pentaerythrytol tetrakis(3-mercaptopropio-nate)	896.4[b]	722.5[b]	8.5E-05[b]	Unlikely irritant; possible sensitizer[b]	Possible mild irritant[b]	Negative[i]	Negative[i]
Sodium dodecyl sulfate	1288[j]	ND	3.900[j]	Irritant[k]	Irritant[b]	Negative[j]	Negative
Gum arabic	ND	ND	ND	ND	ND	ND	Negative[l]
Tetrahydrofuran	1650[m]	127.8[b]	6.10[n]	Irritant[n]	Severe irritant; corrosive[n]	Negative[n]	Possible carcinogen[n]
p-Toluenesulfonic acid	1410[o]	60.3[e]	>10[e]	Irritant[o]	Serious irritant, corrosive[o]	Negative[o]	Negative[o]

Legend:
ND = No data
Key:
a = PubChem 2019a
b = Toxicity Prediction Komputer Assisted Technology (TOPKAT) (BIOVIA™ 2015) model prediction
c = Trochimowicz et al. 2001
d = Melnick et al. 1984
e = TOPKAT database entry
f = PubChem 2019b
g = PubChem 2019c
h = ATSDR 1999
i = Sigma-Aldrich 2014

j = PubChem 2019e
k = Sigma-Aldrich 2018
l = NTP 1982
m = HSDB 2011
n = PubChem 2019f
o = PubChem 2019g

Table 5. Toxicity Assessment

Compound	Oral	Inhalation	Dermal	Ocular	Carcinogenicity	Comments
2-Mercaptobenzo-thiazole	High	High	Mod	Mod	Mod	
Melamine	Low	Low	Low	Mod	Unknown	
Formaldehyde	Mod	Mod	Mod	High	High	
Pentaerythrytol tetrakis(3-mercaptopropionate)	Mod	High	Mod	Low	Low	Possible developmental/ reproductive toxicant
Sodium dodecylsulfate	Mod	Low	Mod	Mod	Low	
Gum Arabic	Low	Low	Low	Low	Low	
Tetrahydrofuran	Mod	Low	Mod	Mod	Mod	
p-Toluenesulfonic acid	Mod	Low	Mod	High	Low	Possible developmental/ reproductive toxicant

Table 6. Ecotoxicity Assessment

Compound	Aquatic	Terrestrial Invertebrates	Terrestrial Plants	Mammals	Birds	Comments
2-Mercaptobenzo-thiazole	Low	Low	Unk	High	Low	
Melamine	Low	ND	ND	Low	ND	
Formaldehyde	Mod	Low	Unk	Mod	Unk	
Pentaerythrytol tetrakis(3-mercaptopropionate)	Low	Mod	Unk	Mod	Unk	
Sodium dodecylsulfate	Mod	Mod	Unk	Mod	Unk	
Gum arabic	Low	Low	Low	Low	Low	
Tetrahydrofuran	Low	Low	Unk	Mod	Unk	
p-Toluenesulfonic acid	Low	Low	Unk	Mod	Unk	

7.3 2-Mercaptobenzothiazole [2-MBT]

7.3.1 General Information

2-MBT (shown in Figure 1), is a pale yellow to tan crystalline powder with a disagreeable odor. Synonyms include 2-benzothiazolethiol, 1,3-benzothiazole-2-thiol, benzothiazolethiol, and captax. The International Union of Pure and Applied Chemistry (IUPAC) name is 3H-1,3-benzothiazole-2-thione. 2-MBT is used as an anti-fungal agent, as a vulcanizing accelerator in rubbers, and to protect copper and copper alloys against corrosion (PubChem 2019, HSDB 2015).

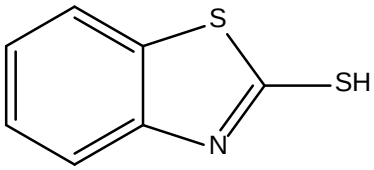

Figure 1. 2-MBT

7.3.2 Toxicology Data

7.3.2.1 Oral

The acute oral LD_{50} is reported to be 100 mg/kg in rats and 1851 mg/kg in mice. This value appears to be inconsistent with other acute toxicity numbers for rats (PubChem 2019a).

TOPKAT modeling predicts an acute oral LD_{50} in rats of 356.9 mg/kg at high confidence, which seems more appropriate although still indicating high oral toxicity.

An experimental LOAEL derived from a National Toxicology Program study (NTP 1988) is reported in the TOPKAT database as 268 mg/kg-day; however, this is inconsistent with the acute LD_{50} reported above.

7.3.2.2 Inhalation

No experimental data were found. TOPKAT predicts an inhalation LC_{50} of 7.5 mg/m^3-hour at low confidence.

7.3.2.3 Dermal

2-MBT is reported to be a skin sensitizer (PubChem 2019a). Contact dermatitis has been reported from exposure to rubber gloves, condoms, and rubber earplugs (HSDB 2015).

7.3.2.4 Ocular

2-MBT is reported to be an ocular irritant (PubChem 2019a).

7.3.2.5 Development and Reproduction

Rodwell et al. (1990) administered 2-MBT by oral gavage to both rats and rabbits. Rats received doses of up to 1800 mg/kg-day in corn oil, and rabbits up to 300 mg/kg-day in 1% methylcellulose. Clinical signs, body weights, and liver weights (rabbits only) were recorded. Maternal effects were produced in rats as evidenced by clinical signs at doses of 1200 and 1800 mg/kg-day and reduced body weight gain and food consumption at 1800 mg/kg-day. In rabbits, maternal effects included slightly reduced body weight gain and increased liver weight at 300 mg/kg-day. In both species, no adverse effects were observed in C-section parameters or in fetal morphological exams. In the rat, a marginal increase in postimplantation loss was considered equivocal at 1800 mg/kg-day; no increase was observed in a 2-MBT range-finding study at dosages up to 2200 mg/kg-day. The NOAEL for developmental toxicity was considered to be 1800 mg/kg-day in the rat and 300 mg/kg-day in the rabbit.

7.3.2.6 Neurotoxicity

Seizures have been reported in animals given 335 mg/kg (HSDB 2015).

7.3.2.7 Genotoxicity

2-MBT was not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537, with or without metabolic activation. In the presence of rat liver S9 fractions, 2-MBT increased the frequency of chromosomal aberrations and sister chromatid exchanges in Chinese hamster ovary cells, as well as mutations at the TK locus of mouse L5178Y lymphoma cells (PubChem 2019a).

An investigation of a possible genotoxic mechanism for carcinogenicity of 2-MBT was conducted by Brewster et al. (1989) by examining the covalent binding of 2-MBT to deoxyribonucleic acid (DNA) from rat tissues. Male and female Fisher 344 rats were dosed via gavage with 375 mg/kg body weight of radiolabeled 2-MBT. Eight hours after dosing, the liver, adrenal gland, pancreas, pituitary gland, and femur were harvested from each animal. Assay results from liver demonstrated only 0.6% of the 2-MBT radioactivity, while the other tissues exhibited less than 0.03% of the administered dose. These results suggest 2-MBT does not significantly bind to DNA.

7.3.2.8 Carcinogenicity

2-MBT is considered to be a possible human carcinogen (PubChem 2019a).

Epidemiological studies by Whittaker et al. (2004) indicate workers exposed to 2-MBT have an increased risk of bladder cancer. Review of the epidemiological and toxicological dataset for 2-MBT indicated induction of renal pelvis transitional cell tumors is the most sensitive and relevant

health effects endpoint. A Total Allowable Concentration (TAC) in drinking water of 600 µg/L was derived for 2-MBT.

7.3.2.9 Ecotoxicology

7.3.2.9.1 Fate and Transport

If released to soil, 2-MBT is expected to have low to moderate mobility based upon a measured K_{oc} range of 326–3560 (log K_{oc} 2.51–3.55). The pKa of 2-MBT is 7.03, indicating that this compound will exist partially in the anion form in the environment. Compared to their neutral counterparts, anions generally do not adsorb more strongly to soils containing organic carbon and clay. Volatilization from moist soil surfaces is not expected to be an important fate process based upon an estimated Henry's Law constant of 4.1 $x10^{-11}$ atm-m^3/mol. Based upon its vapor pressure, 2-MBT is not expected to volatilize from dry soil surfaces (PubChem 2019a).

If released to air, a vapor pressure of 2.25 x 10^{-8} mm Hg at 20ºC indicates 2-MBT will exist in both the vapor and particulate phases in the atmosphere. Vapor-phase 2-MBT will be degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 9.5 hours. Particulate-phase 2-MBT will be removed from the atmosphere by wet and dry deposition. 2-MBT absorbs at wavelengths >290 nm and, therefore, may be susceptible to direct photolysis by sunlight (PubChem 2019a).

A bioconcentration factor (BCF) of <8 for 2-MBT was measured in fish, using carp (*Cyprinus carpio*) which were exposed over a 6-week period. This BCF suggests the potential for bioconcentration in aquatic organisms is low (PubChem 2019a).

7.3.2.9.2 Ecotoxicity

2-MBT is reported to be very toxic to aquatic life with long-term effects (PubChem 2019a).

The 48-hour LC_{50} in water flea (*Ceriodaphnia dubia*) is reported to be 4.190 mg/L, and the 96-hour LC_{50} for bluegill (*Lepomis macrochirus*) is 1.900 mg/L. The 96-hour LC_{50} for rainbow trout (*Oncorhynchus mykiss*) is 0.420 mg/L, and the 96-hour LC_{50} for channel catfish (*Ictalurus punctatus*) is 1.650 mg/L (PubChem 2019a).

When administered to birds as a gavage bolus, 2-MBT is almost non-toxic; it is only slightly toxic to birds when added to their food and consumed in a less concentrated form. 2-MBT is considered highly toxic to freshwater fish and moderately toxic to freshwater invertebrates (HSDB 2015).

2-MBT is toxic to activated sludges, impacting degradation. A bacteriostatic effect was observed towards *E. coli*, *Sarcina lutea*, *Staphylococcus aureus*, and a 2-hydroxybenzothiazole-degrading isolate. 2-MBT caused membrane disturbances as measured by induced potassium effluxes from the cell. It appears 2-MBT interferes with an oxidoreduction step in membrane-bound systems and probably also interferes with metabolic reactions not related to the respiratory chain (DeWever et al. 1997).

7.3.2.9.3 Degradation/Treatment

Results of biodegradation screening tests indicate that 2-MBT is resistant to environmental biodegradation and not readily biodegradable in soil or water. Photodegradation can occur on soil surfaces exposed to sunlight (PubChem 2019a).

7.4 Melamine

7.4.1 General Information

Melamine (shown in Figure 2) exists as colorless to white monoclinic crystals, prisms, or as a white powder. The IUPAC name is 1,3,5-triazine-2,4,6-triamine (PubChem 2019b). Melamine's primary industrial use is in the preparation of melamine resins used in preparation of melamine-formaldehyde synthetics for items such as laminates, glues, molding compounds, flame retardants and super-plasticizers for concrete, among other applications (Organization for Economic Cooperation and Development (OECD) 1999). Melamine is sometimes illegally added to food products in order to increase the apparent protein content, but new instrumental methods of analysis have greatly reduced this occurrence (PubChem 2019b). Melamine was added to pet food in 2007, resulting in several deaths. Infant formula was also found to be contaminated with melamine and the related compound, cyanuric acid. Only traces of melamine and cyanuric acid were found in infant formula sold in the U.S., but in China, 50,000 infants were hospitalized after consuming adulterated infant formula, and at least 4 died. It has also been demonstrated that melamine present in feed for milk cows will appear in the milk within 8 hours of administration (Cruywagen et al. 2009).

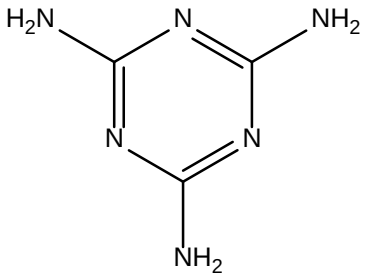

Figure 2. Melamine

7.4.2 Toxicology Data

7.4.2.1 Oral

Observed toxic effects of melamine alone in animals in controlled studies occur only after high-dose exposures. All information to date indicates melamine is metabolically inert. Kidney problems associated with melamine ingestion appear to result from formation of crystals in the kidney, usually in conjunction with melamine-related compounds, such as cyanuric acid, that are commonly present as contaminants in melamine formulations. This crystal formation has been

shown to take place at various dose levels and is a threshold- and concentration-dependent phenomenon.

The acute oral LD_{50} in rats is 3160 mg/kg for males and 3850 mg/kg for females (Trochimowicz et al. 2001).

The acute oral LD_{50} in mice is 4550 mg/kg. Signs of toxicity following lethal doses include lacrymation, dyspnea, intermittent tremors, and coma preceding death. Vasodilation in tail and ears, and paralysis of forequarters were also observed (Trochimowicz et al. 2001).

In dogs given a single oral dose of 2400 mg/kg, melamine produced diuresis and crystalluria. Dimelamine monophosphate was found as a urinary product (Trochimowicz et al. 2001).

Pet food adulterated with melamine has resulted in renal failure in dogs and cats. Affected animals exhibit uremia, anorexia, vomiting, lethargy, polyuria, azotemia, and hyperphosphatemia. Distal tubular lesions were present in affected animals, and unique polarizable crystals with striations were present in distal tubules or collecting ducts; proximal tubules were largely unaffected. The concentrations of melamine that produce these effects are not known (Brown et al. 2007).

Melamine was administered orally in feed to male Fisher 344 rats at doses equivalent to 63-1267 mg/kg for 4 weeks. The study was conducted to evaluate urolithiasis (formation of urinary calculi) induction by melamine. In-life observation indicated a significant dose-related depression in body weight gain, elevated water intake, and altered food consumption pattern. Melamine produced a dose-dependent incidence of urinary calculi and urinary bladder hyperplasia. With one exception, all animals (40 per group) with hyperplasia had calculi. The NOAEL was determined to be equivalent to 63 mg/kg-day (OECD 1999).

Melamine produced strong diuretic effects in rat and dogs fed 126 mg/kg daily for 1 to 4 weeks. No histopathological effects were seen (Trochimowicz et al. 2001).

Melamine was administered in the diet to F344 rats or B6C3F1 mice for 13 weeks. The dose levels ranged from 750–18,000 ppm (mg/kg) for rats and 6000–18,000 ppm (mg/kg) for mice. Compound-related lesions were observed in the urinary tract. Most noticeable was the development of uroliths (urinary bladder stones), which occurred at a greater frequency in males than females of either species. Increased incidence of urinary bladder stones and hyperplasia of the bladder epithelium were observed in male rats (Melnick et al. 1984).

Chronic feeding studies were carried out over a 2-year period at a dietary level of 1000 ppm without ill effect. Dogs received melamine at 30,000 ppm in their feed for a period of 1 year. After 60–90 days, the dogs showed melamine crystalluria, which persisted throughout the remainder of the 1-year observation. At autopsy, gross and microscopic examination of tissues revealed no abnormality attributable to the feeding of melamine (Trochimowicz et al. 2001).

Melamine was administered in feed to F344 rats or B6C3F1 mice for 103 weeks. Dose levels were 2250 or 4500 ppm for male rats and mice of both sexes; female rats received 4500 or 9000 ppm. Compound-related lesions were observed in the urinary tract. Most noticeable was

the development of uroliths, which occurred at a greater frequency in males than in females of either species. Transitional cell carcinomas in the urinary bladder of male rats occurred at a significantly higher incidence ($p \leq 0.016$) in the 4500 ppm group (8/49) than in the controls (0/45). Seven of the eight male rats with transitional-cell carcinomas of the urinary bladder also had bladder stones. There was a statistically-significant association ($p \leq 0.001$) between bladder stones and bladder tumors in male rats fed melamine at the high dose. Urinary bladder tumors were not observed in the low-dose male rat group; bladder stones were observed in one rat. Chronic inflammation of the kidney was observed in female rats at both dose levels (Melnick et al. 1984, NTP 1983).

7.4.2.2 Inhalation

No experimental data were found. TOPKAT modeling predicts an acute inhalation LC_{50} of 1500 g/m^3-hour at high confidence, indicating lack of direct toxicity. Thermal decomposition results in production of toxic nitrogen oxides and hydrogen cyanide (HSDB 2012).

7.4.2.3 Dermal

Human subjects given patch tests with melamine showed no evidence of irritation or sensitization (PubChem 2019b).

The dermal LD_{50} for rabbits is greater than 1000 mg/kg, indicating no dermal toxicity (HSDB 2012).

Application of melamine to rabbit skin caused no primary skin irritation or signs of systemic toxicity when applied under an impervious cover at doses as high as 1 g/kg for 18 hours (Trochimowicz et al. 2001).

Melamine applied under a rubber cuff to guinea pig skin as a 1% solution in water produced little to no irritation (Trochimowicz et al. 2001).

7.4.2.4 Ocular

An entry in the TOPKAT database indicates melamine is a mild ocular irritant.

7.4.2.5 Development and Reproduction

Female Wistar rats received melamine orally in feed at doses of 1500, 4500, and 15,000 ppm. Administration of melamine during organogenesis showed signs of maternal toxicity only at 15,000 ppm, along with reduced food consumption, body weight loss, reduced body weight gain, and corrected body weight gain. Maternal symptoms included hematuria (23/25 animals), indrawn flanks (7/25 animals) and piloerection (1/25 animals), but maternal symptoms were reversed upon stopping treatment. Melamine appeared to have no influence on gestational parameters, and showed no signs of developmental toxicity. There were no signs of teratogenicity at doses up to and including 15,000 ppm (European Chemicals Board (ECB) 2007).

7.4.2.6 Neurotoxicity

An and Sun (2017) recently published a review addressing neurotoxicity of melamine. Melamine appears to represent a neurological hazard only during development. Animal studies indicate melamine can transit the blood-brain barrier and the placenta. Experimental observations have included an increase in reactive oxygen species, apoptosis, hyperpolarization, spontaneous neuronal firing, and disrupted metabolism. Melamine can also apparently affect the central nervous system (CNS) and has induced deficits in learning and memory in adolescent rats.

7.4.2.7 Genotoxicity

Melamine tested negative in Ames *Salmonella typhimurium* strains TA100, TA98, TA97, and TA102, with or without microsomal (S9) activation, at concentrations up to 5000 µg/plate (ECB 2007). Melamine was also negative in strains TA1535 and TA1537, with or without microsomal activation (IARC 1986).

Increased numbers of micronuclei were not observed in CD-1 mice receiving melamine at 1000 mg/kg-day either 30 or 48 hours after dosing, or after receiving 2 doses 24 hours apart and sacrificed after 48 or 72 hours (ECB 2007).

Melamine tested negative in Chinese hamster ovary (CHO) cells with or without microsomal activation at concentrations of 0, 240, 270, or 300 µg/mL (ECB 2007).

Melamine was negative in the HGPRT forward mutation assay in CHO cells at concentrations from 600 to 1000 µg/mL (ECB 2007).

Melamine also tested negative in the L5178Y tk+/- mouse lymphoma forward mutation assay. Cultures were exposed for 4 hours then cultured for 2 days before plating on soft agar, with or without trifluorothymidine, 3 µg/mL (McGregor et al. 1988).

Sex-linked recessive dominant lethal mutations were not induced in *Drosophila melanogaster* given melamine in the diet (IARC 1986).

7.4.2.8 Carcinogenicity

Melamine is not classifiable as to its carcinogenicity in humans (PubChem 2019b).

In animals, melamine produces urinary bladder tumors via a non-DNA-reactive mechanism under conditions when bladder calculi were produced in male rats. The effective daily dose to induce tumors in 50% of the test animals (TD_{50}) has been calculated to be 735 mg/kg-day. Only male rats have been demonstrated to produce tumors; no tumors were found in female rats or in mice of either gender (CPDB 2007, HSDB 2009).

7.4.2.9 Ecotoxicology

7.4.2.9.1 Fate and Transport

If released to soil, melamine is expected to have very high mobility based upon an estimated K_{oc} of 5. Volatilization from moist soil surfaces is not expected to be an important fate process based upon an estimated Henry's Law constant of 1.8×10^{-14} atm-m^3/mol. If released into water, melamine is not expected to adsorb to suspended solids and sediment based upon the estimated K_{oc}. Volatilization from water surfaces is not expected to be an important fate process based upon this compound's estimated K_H. An estimated BCF of 3 suggests bioconcentration in aquatic organisms is low. If released to air, a vapor pressure of 3.59×10^{-10} mmHg at 20ºC indicates melamine will exist solely in the particulate phase in the atmosphere. Particulate-phase melamine will be removed from the atmosphere by wet or dry deposition (PubChem 2019b).

7.4.2.9.2 Ecotoxicity

Melamine-cyanuric acid crystals have been shown to develop in mice, pig, cat, and fish kidneys, when test animals are dosed with both melamine and its analogue cyanuric acid. The crystals that form in pigs and fish are identical to those seen in cats (U.S. Food and Drug Administration (FDA) 2018).

The EPA's ECOSAR program models melamine as both a melamine and an amino-meta aniline. The minimum 96-hour LC_{50} in green algae is 2.78 mg/L, the minimum 48-hour LC_{50} in *Daphnia* is 6.23 mg/L, and the minimum 96-hour LC_{50} in fish is 391 mg/L.

Exposure of the bloodfluke *Biomphalaria glabrata* for 45 days to sublethal concentrations (500, 1000 and 2000 mg/L) of melamine in water caused a concentration-dependent decrease in reproductive ability (Ramusino & Tenconi 1980).

Melamine at 500 and 1000 mg/L lowered the rate of Rainbow trout (*Salmo gairdneri*) egg hatchability and produced increased incidence of exposed larvae at 125 and 250 mg/L (Ramusino & Vailati 1982).

Fish and pigs were fed targeted doses of melamine (400 mg/kg), cyanuric acid (400 mg/kg) or melamine and cyanuric acid (400 mg/kg of each compound) for 3 days and euthanized 1, 3, 6, 10 or 14 days after administration ceased. Fresh, frozen, and formalin-fixed kidneys were examined for crystals. Edible tissues were collected for residue analysis. All animals fed the combination of melamine and cyanuric acid developed gold-brown renal crystals of radial sphere pattern similar to those detected in cats. Melamine and cyanuric acid residues were identified in edible tissues of fish (Reimschuessel et al. 2008).

Between November 2003 and September 2006, 300 to 400 45-to-60-day-old, farm-kept Iberian piglets developed anorexia, polydipsia, and lethargy. Piglets were from five different farms in western Spain. Morbidity was between 40% and 60%, and mortality ranged from 20–40 percent of the total population of post-weaning piglets. Postmortem examinations of nine animals found their kidneys to be enlarged with yellow foci in the cortex and medulla. Microscopically, crystals were observed within the lumina of dilated distal tubules and collecting ducts, causing flattening of the renal tubular epithelial cells. Toxicologic analysis of fixed kidney tissues from four piglets

found the presence of melamine and related compounds. Melamine concentrations were determined to be 9200–29,000 mg/kg (Gonzalez et al. 2009).

7.4.2.9.3 Degradation/Treatment

No biodegradation of melamine using a standard 5-day Biological Oxygen Demand (BOD) test was observed, suggesting that biodegradation may not be an important environmental fate process. Hydrolysis is not expected to be an important environmental fate process since this compound lacks functional groups that hydrolyze under environmental conditions (PubChem 2019b).

7.5 Formaldehyde

7.5.1 General Information

Formaldehyde (shown in Figure 3) is a colorless poisonous gas with a wide range of uses, including the manufacture of resins and textiles, as a disinfectant, and as a laboratory fixative or preservative. Synonyms include formalin (10% solution), methanal, formol, formic anhydride, oxomethane, and others. Formaldehyde is a Standardized Chemical Allergen that functions via increased histamine release and cell-mediated immunity. Formaldehyde is readily soluble in water; a 10% solution is typically used as a disinfectant and to preserve biological specimens. Environmentally, formaldehyde is found in the atmosphere, smoke from fires, automobile exhaust, and cigarette smoke. Small amounts are produced during normal metabolic processes in most organisms, including humans (PubChem 2019c).

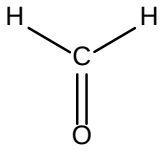

Figure 3. Formaldehyde

7.5.2 Toxicology Data

Effects of formaldehyde have been discussed extensively in ATSDR's *Toxicological Profile of Formaldehyde* (ATSDR 1999) and a subsequent *Addendum* (ATSDR 2010).

7.5.2.1 Oral

The acute oral LD_{50} in rats is reported to be 800 mg/kg; the corresponding value in the mouse is 42 mg/kg (PubChem 2019c).

Formaldehyde poses an acute oral toxicity hazard. The lowest lethal dose for humans taking formaldehyde orally is 36 mg/kg (PubChem 2019c). The ATSDR noted there were no effects in animals receiving less than 49 mg/kg-day (ATSDR 2010).

7.5.2.2 Inhalation

Controlled-exposure human studies have found that short-term inhalation exposures to concentrations ranging from 0.4 to 3 ppm can produce symptoms of mild to moderate irritation of the eyes, nose, and throat (ATSDR 2010).

The acute inhalation LC_{50} in rats for a 4-hour exposure is reported to be 1070 mg/m^3 (PubChem 2019c).

Formaldehyde is harmful if inhaled and may cause allergy or asthma symptoms or breathing difficulties if inhaled. Evidence of sensitization has been reported. Inhalation of high concentrations may cause lung edema but only after initial corrosive effects have become apparent on the eyes and the upper respiratory tract (PubChem 2019c).

7.5.2.3 Dermal

Formaldehyde causes dermal irritation and is likely a dermal sensitizer (PubChem 2019). A fraction (usually < 5%) of individuals exposed via patch testing or similar challenge typically are positive (ATSDR 1999).

7.5.2.4 Ocular

Formaldehyde causes serious eye damage (PubChem 2019c). Exposure to formaldehyde in the atmosphere at concentrations in the range 0.4–3.0 ppm and above can cause eye irritation (ATSDR 1999).

7.5.2.5 Development and Reproduction

Developmental effects have not been observed in animal studies with formaldehyde (PubChem 2019c).

Reports of higher rates of spontaneous abortion in female occupational workers have been characterized as inconsistent, and effects on pregnancy and fetal development in animals were not seen below maternally toxic concentrations (ATSDR 2010).

7.5.2.6 Neurotoxicity

Experiments in humans by Bach and colleagues have demonstrated decreased performance in tests designed to access distractibility, short-term memory, and the capability to understand and perform certain tasks. Decreased performance was correlated with increasing exposure to formaldehyde (ATSDR 2010).

7.5.2.7 Genotoxicity

Formaldehyde has been demonstrated to cause aneuploidy and structural chromosome alterations in cultured myeloid progenitor cells. The level of chromosome alterations followed a pattern frequently observed in acute myeloid leukemia and may indicate a potential mechanism underlying formaldehyde-induced leukemogenesis (Lan et al. 2015).

Obe and Beek (1979) found formaldehyde induced a 1.5- to 3-fold increase in Sister Chromatid Exchange in human lymphocytes in culture.

A majority of genotoxicity tests show that formaldehyde can induce genotoxic effects in various organisms and cell types. Environment Canada/Health Canada and the WHO have concluded formaldehyde is a weak genotoxic (ATSDR 2010b).

7.5.2.8 Carcinogenicity

Formaldehyde is a classified by the ATSDR, EPA, and American Conference of Governmental Industrial Hygienists® (ACGIH®) as a probable human carcinogen based on limited evidence in humans and sufficient evidence in animals. The IARC considers there to be sufficient evidence in humans (PubChem 2019c).

In its 2006 monograph, the IARC concluded that the overall evidence in humans does not support a causal role for formaldehyde in cancers of the respiratory tract. However, the IARC does believe there is sufficient causal evidence for association of formaldehyde with leukemia (ATSDR 2010b).

7.5.2.9 Ecotoxicology

7.5.2.9.1 Fate and Transport

The fate of formaldehyde in soil is not fully understood, but the compound is biodegradable to carbon dioxide and water or formic acid under both aerobic and anaerobic conditions. Formaldehyde is also biologically active, reacting readily with phenol, amine, amide, sulfide, purine, and pyrimidine functional groups. Formaldehyde is also subject to spontaneous polymerization (ATSDR 2010b).

In air, formaldehyde reacts with NO_3 radicals with a lifetime of 83 days (Atkinson & Arey 2003).

7.5.2.9.2 Ecotoxicity

There is an extensive amount of formaldehyde toxicity information in the EPA ECOTOX database (EPA 2019). Four-day EC_{50} levels for green algae are in the range of 0.7–3.3 mg/L, 48-hour EC_{50} levels in *Daphnia* range from 6 to 30 mg/L, and the 96-hour LC_{50} in the standard fish test species (fathead minnow, *Pimephalas promelas*, and rainbow trout, *Oncorhynchus mykiss*) ranges from 2 to 550 mg/L. These values generally place formaldehyde in the moderately toxic category, comparable to GHS Categories I and II.

7.5.2.9.3 Degradation/Treatment

Uncatalyzed decomposition is very slow below 300ºC; extrapolation of kinetic data to 400ºC indicates rate of decomposition is about 0.44 percent/min at 1 atm (PubChem 2019c).

7.6 Pentaerythrytol tetrakis(3-mercaptopropionate) [PTT]

7.6.1 General Information

PTT (shown in Figure 4) is a clear, colorless viscous liquid with a sulfur stench (Sigma-Aldrich 2014). The IUPAC name for PTT is [3-(3-sulfanylpropanoyloxy)-2,2-bis(3-sulfanylpropanoyl-oxymethyl)propyl] 3-sulfanylpropanoate (PubChem 2019d). Other systematic names for this compound are 3-mercapto-1,1'-(2,2-bis((3-mercapto-1-oxopropoxy)methyl-1,3-propanediyl) propanoic acid ester and 3-mercapto-2,2-bis((3-mercapto-1-oxopropoxy)methyl)-1,3-propandiyl propanoic acid ester (ChemIDPlus 2019).

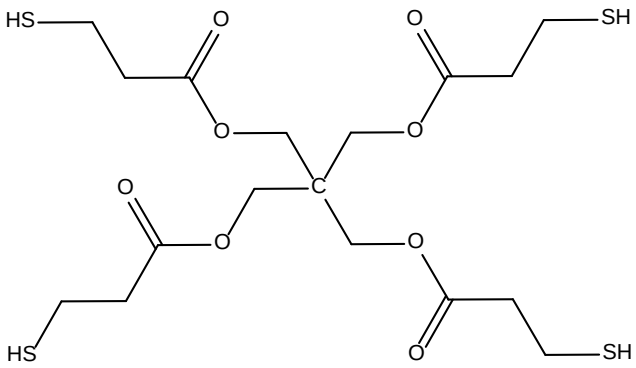

Figure 4. PTT

7.6.2 Toxicology Data

7.6.2.1 Oral

A supplier safety data sheet categorizes PTT in GHS Category 4; the acute oral LD_{50} in female rats is reported to be 1000–2000 mg/kg (Sigma-Aldrich 2014). Overall, PTT is assessed to be moderately toxic.

TOPKAT modeling predicts an acute oral LD_{50} in rats of 896.4 mg/kg at low confidence. The chronic LOAEL is predicted to be 722.5 mg/kg-day at high confidence.

7.6.2.2 Inhalation

No experimental data are available. TOPKAT modeling predicts an acute inhalation LC_{50} in rats of 85.8 µg/m^3-hour (an unreasonably low number) at low confidence. This is an extreme level of toxicity not typically associated with chemical compounds and not likely to be accurate. It is also unlikely to be of importance since the probability of inhalation exposure is low.

7.6.2.3 Dermal

PTT is reported to possibly be a skin sensitizer (PubChem 2019d). A supplier safety data sheet categorizes PTT in GHS Category 1 (Sigma-Aldrich 2014).

TOPKAT modeling predicts PTT is an unlikely irritant but a possible severe sensitizer.

7.6.2.4 Ocular

No eye irritation was reported in an experimental evaluation in the rabbit, conducted in accordance with OECD Guideline 405 (Sigma-Aldrich 2014).

TOPKAT modeling predicts PTT will possibly be a mild irritant.

7.6.2.5 Development and Reproduction

No experimental data were found. TOPKAT modeling predicts PTT will be a developmental or reproductive toxicant at low confidence.

7.6.2.6 Neurotoxicity

No information on neurotoxicity was found.

7.6.2.7 Genotoxicity

Tests in mammalian and bacterial cell cultures were reportedly negative (Sigma-Aldrich 2014).

7.6.2.8 Carcinogenicity

PTT is not listed as carcinogenic by the IARC, ACGIH, NTP, or OSHA (Sigma-Aldrich 2014).

7.6.2.9 Ecotoxicology

7.6.2.9.1 Fate and Transport

If released to soil, PTT is expected to have a low mobility in groundwater due to limited solubility, and it is unlikely to pose a hazard to surface or drinking water. Partition from water or wet surfaces is expected to be insignificant due to a calculated K_H of 3.62×10^{-17} atm-m^3/mol. Vaporization from dry surfaces is also expected to be insignificant due to vapor pressure, so any

PTT present in the atmosphere will be present in particulate form. Tendency to bioaccumulate is expected to be low.

7.6.2.9.2 Ecotoxicity

PTT is classified as “very toxic to aquatic life with long lasting effects” by the GHS (PubChem 2019d). A supplier safety data sheet categorizes PTT in GHS Category I for acute aquatic toxicity and chronic aquatic toxicity (Sigma-Aldrich 2014).

The EC_{50} for a 72-hour test in the green algae *Desmodesmus subspicatus* was greater than 0.12 mg/L. The 96-hour LC_{50} in rainbow trout (*Oncorhynchus mykiss*) was 0.42 mg/L (Sigma-Aldrich 2014).

The EPA’s ECOSAR program models PTT in the thiol/mercaptan class. The 96-hour EC_{50} in green algae is predicted to be 0.919 mg/L, the 48-hour LC_{50} in *Daphnia* is predicted to be 1.26 mg/L, and the 96-hour LC_{50} in fish is predicted to be 7.07 mg/L. The prediction for green algae drives the GHS classification for acute toxicity to Category I.

7.6.2.9.3 Degradation/Treatment

PTT is not predicted to be biodegradable according to the EPA’s Estimation Programs Interface (EPI) Suite 2.0 models (EPA 2018); environmental persistence is projected to be weeks to months.

According to the EPA’s EPI Suite models, PTT will be poorly removed (< 3.5%) by physical processes at wastewater treatment plants.

7.7 Sodium dodecyl sulfate [SDS]

7.7.1 General Information

SDS, also known as sodium lauryl sulfate, is an anionic surfactant. It is a white to pale yellow solid with a mild odor. Its alternative CAS numbers are 1335-72-4 and 8012-56-4 (PubChem 2019e). Figure 5 illustrates the molecular structure of SDS.

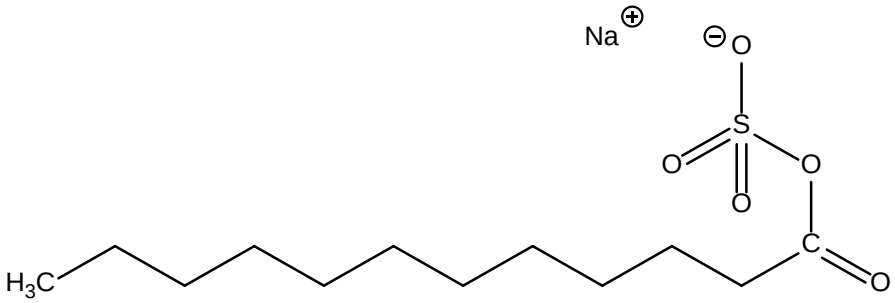

Figure 5. SDS

7.7.2 Toxicology Data

7.7.2.1 Oral

The acute oral LD_{50} in rats is reported to be 1288 mg/kg, corresponding to GHS Category 4. Ingestion of large amounts causes irritation of the stomach (PubChem 2019e).

7.7.2.2 Inhalation

The acute inhalation LC_{50} in rats is reported to be 3900 mg/m^3-hour, corresponding the GHS inhalation Category 4. Inhalation of dust causes sneezing and coughing (PubChem 2019e).

7.7.2.3 Dermal

The LD_{Lo} for dermal toxicity in the rabbit is 10,000 mg/kg. Effects from overexposure include ataxia, changes is structure or function of salivary glands, gastric hypermobility, and diarrhea. Contact with skin causes some irritation (PubChem 2019e).

According to a supplier safety data sheet, SDS is a GHS Category 2 skin irritant (Sigma-Aldrich 2018).

7.7.2.4 Ocular

Dust irritates the eyes and may cause burns on prolonged contact (PubChem 2019e). According to a supplier safety data sheet, SDS is classified as a GHS Category 1 eye irritant (Sigma-Aldrich 2018).

7.7.2.5 Development and Reproduction

No data were found. SDS is not expected to be a developmental or reproductive toxicant.

7.7.2.6 Neurotoxicity

No data were found.

7.7.2.7 Genotoxicity

SDS tests negative in the Ames test for mutagenicity with and without microsomal activation in all five standard test strains of *S. typhimurium*. SDS also tests negative in the micronucleus assay, the sister chromatid exchange assay in Chinese hamster ovary cells, and the mouse lymphoma cell forward mutation assay with and without activation (PubChem 2019d).

7.7.2.8 Carcinogenicity

SDS is not expected to be carcinogenic.

7.7.2.9 Ecotoxicology

7.7.2.9.1 Fate and Transport

If released to soil, SDS is expected to have slight mobility based upon an estimated K_{oc} of 3200. Volatilization from moist soil surfaces or water is not expected to be an important fate process based upon a water solubility of 1.00 $x10^5$ mg/L and because it is a salt. Based upon its estimate vapor pressure, SDS is not expected to volatilize from dry soil surfaces (HSDB 2000).

If SDS is released to air, an estimated vapor pressure of 4.7 x 10^{-13} mm Hg at 25 ºC indicates the compound will exist solely in the particulate phase in the ambient atmosphere. Particulate-phase SDS will be removed from the atmosphere by wet and dry deposition. SDS does not contain chromophores that absorb at wavelengths >290 nm and, therefore, is not expected to be susceptible to direct photolysis by sunlight (HSDB 2000).

An estimated BCF of 71 suggests the potential for SDS bioconcentration in aquatic organisms is moderate (HSDB 2000).

7.7.2.9.2 Ecotoxicity

The 48-hour EC_{50} in *Daphnia* is reported to be 1.8 to 51.5 mg/L. The 96-hour LC_{50} for eastern mosquitofish (*Gambusia holbrooki*) is reported to be 15.1 mg/L (PubChem 2019e).

According to a supplier safety data sheet, SDS is classified in GHS Category II for acute aquatic toxicity and Category III for chronic aquatic toxicity (Sigma-Aldrich 2018).

7.7.2.9.3 Degradation/Treatment

Abiotic degradation is not expected to be an important environmental fate process for SDS due to lack of hydrolysable functional groups (PubChem 2019e).

SDS is 95% biodegradable within 28 days under aerobic conditions (Sigma-Aldrich 2018).

7.8 Gum arabic [Acacia]

7.8.1 General Information

Gum arabic, also known as acacia, is a white to yellow-brown powder. Chemically, gum arabic is a polysaccharide composed primarily of arabinose, rhamnose, galactose, and glucuronic acid with calcium, magnesium, and potassium ions. Its primary use is as a food additive, and it is generally recognized as safe (GRAS). It is also used for relief of inflammation and as a suspending or dispersing agent. Obtained from trees of the genus *Acacia*, gum arabic is the result of an infection, either bacterial or fungal. It is exuded only by unhealthy trees; heat, poor nutrition, and drought stimulate its production (HSDB 2002)

7.8.2 Toxicology Data

Workers exposed to gum arabic have been found to suffer from an allergic condition known as "printer's asthma," characterized by difficulty breathing. Frequency of allergic symptoms depends primarily on the atmospheric gum arabic concentration. Since gum arabic is no longer generally used in printing, having been supplanted by chalk, the incidence of this allergic condition is significantly reduced (HSDB 2002).

7.8.2.1 Oral

Ingested orally, acacia is non-toxic; it is recognized as a GRAS food additive (HSDB 2002).

7.8.2.2 Inhalation

Although gum arabic is non-toxic by inhalation, sensitivity can develop over time (HSDB 2002).

7.8.2.3 Dermal

No data were found.

7.8.2.4 Ocular

No data were found.

7.8.2.5 Development and Reproduction

No data were found.

7.8.2.6 Neurotoxicity

No data were found.

7.8.2.7 Genotoxicity

No data were found.

7.8.2.7 Carcinogenicity

A 2-year study by the NTP found that gum arabic was not carcinogenic in rats or mice (NTP 1982).

7.8.2.8 Ecotoxicology

7.8.2.8.1 Fate and Transport

Although highly soluble in water, gum arabic is a high-molecular-weight polymer and thus not expected to be highly mobile in the environment.

7.8.2.8.2 Ecotoxicity

Gum arabic is not anticipated to cause ecotoxicity.

7.8.2.8.3 Degradation/Treatment

As a naturally-produced polysaccharide, gum arabic is expected to be biodegradable.

7.9 Tetrahydrofuran [THF]

7.9.1 General Information

THF, also known by its IUPAC name, oxolane, is a clear, colorless liquid with an ethereal odor. It is used as a solvent in many applications, including various polymers, and in the preparation of inks, lacquers, and coatings, especially for vinyl polymers (PubChem 2019f). Figure 6 illustrates the molecular structure of THF.

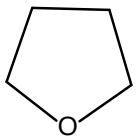

Figure 6. THF

7.9.2 Toxicology Data

7.9.2.1 Oral

The acute oral LD_{50} is reported to be 1650 mg/kg in rats, 2300 mg/kg in mice, and 2300 mg/kg in the guinea pig. The probable oral lethal dose in humans is 50–500 mg/kg (HSDB 2011).

TOPKAT modeling predicts a chronic LOAEL of 127.8 mg/kg at high confidence.

7.9.2.2 Inhalation

The acute inhalation LC_{50} in the rat is reported to be 18,000 to 22,000 ppm for a 4-hour exposure, and 1200 ppm in rabbits for a 4-hour exposure. THF may cause respiratory irritation. Its vapors cause nausea, dizziness, headache, and loss of conciousness (PubChem 2019f). The margin of safety between anesthesia and death is small (HSDB 2011).

Conversion factor: 1 ppm = 2.95 mg/m^3 (NIOSH 2018).

7.9.2.3 Dermal

THF is well absorbed through the skin of rabbits and rats. Dermal exposure results in dry skin,

redness, and pain. THF was rapidly lethal to rats when 10 percent of their body surface was exposed to the liquid solvent (PubChem 2019f).

7.9.2.4 Ocular

THF causes serious eye irritation and damage (PubChem 2019f).

7.9.2.5 Development and Reproduction

Mast et al. (1992) exposed rats and mice to THF at doses up to 5000 ppm by inhalation for 6 hours/day, 7 days a week from Gestation Day (GD) 6–19 for rats and GD 6–17 for mice. Body weights of dams in the 5000-ppm dose group were reduced at euthanization. There were no effects on the percentage of live rat fetuses/litter or on the fetal sex ratio. Fetal body weight was significantly reduced for the 5000-ppm group, but the incidence of abnormalities was not increased. The mean body and uterine weights of mice were reduced for the 1800- and 5000-ppm groups at euthanization, but adjusted maternal weight gain was not affected at 1800 ppm. There was a reduction in the percentage of live fetuses/litter for the mice at 1800 and 5000 ppm (95% resorbtions in the 5000-ppm group). Fetal weight and sex ratio in mice were not affected. An increase in the incidence of reduced sternebral ossifications was correlated to the THF concentration although differences between groups were not statistically significant. There were no increases in the incidences of other malformations or variations. These results suggest that THF may be embryotoxic in mice, but if the conceptus survives, development continues in the normal fashion. The NOAEL for maternal toxicity was 1800 ppm in both rats and mice. The NOAEL for developmental toxicity was 1800 ppm in rats and 600 ppm in mice.

7.9.2.6 Neurotoxicity

Rats given intraperitoneal injections of THF reacted with slight confusion and slowness to react that lasted for about 10 minutes at 10 minutes after the injection. Repetition of the treatment the following day showed no further CNS depression. With doses increasing up to 2230 mg/kg, CNS depression lasted about 6 hours. With repeated injections at this concentration, the same CNS depression was observed, the overall condition deteriorated, and death occurred in one animal after the third injection (HSDB 2011).

Werawattanachai et al. (2007) exposed laboratory animals to THF and then evaluated them in a neurobehavioral test. Decreased performance was observed in the righting reflex and the rotarod test. While some of the mechanisms of the THF actions on the CNS appear likely to involve direct or indirect interactions with the GABA-B receptor, some differences in qualitative and quantitative pharmacology suggest other mechanisms are also likely involved in the observed neurobehavioral effects of these selected doses of THF in mice.

7.9.2.7 Genotoxicity

THF is negative in the Ames test, the *E. coli* reverse mutation assay with *E. coli WP 2* up to 20 µL/plate with or without microsomal activation, the Sister Chromatid Exchange assay with CHO-W-B1 at 500-5000 µL with and without microsomal activation, and the micronucleus assay in mice (PubChem 2019g).

THF did not induce unscheduled DNA synthesis in rat hepatocytes (PubChem 2019f).

7.9.2.8 Carcinogenicity

THF is suspected of being carcinogenic. The ACGIH considers THF a confirmed animal carcinogen with unknown relevance to humans (PubChem 2019f).

The NTP conducted a 102-week study by inhalation in male and female rats and mice at exposures of 0, 200, 600, or 1800 ppm, 6 hours/day, 5 days/week. There was some evidence of carcinogenicity in male rats based on increased incidences of renal tubule adenoma or carcinoma (combined). There was no evidence of carcinogenic activity in female rats or male mice. There was clear evidence of carcinogenic activity in female mice based on increased incidence of hepatocellular neoplasms (NTP 1998).

7.9.2.8 Ecotoxicology

7.9.2.8.1 Fate and Transport

If released to soil, THF is expected to have very high mobility based upon K_{oc} values of 18 and 23. If released into water, THF is not expected to adsorb to suspended solids and sediment, based upon the K_{oc} values. Volatilization from water or wet soil is expected to be an important fate process based upon this compound's K_H of 7.05 x 10^{-5} atm-m^3/mol. Based upon its vapor pressure, THF may volatilize from dry soil surfaces. If released to air, a vapor pressure of 162 mm Hg at 25ºC indicates THF will exist solely as a vapor in the atmosphere. An estimated BCF of 3 suggests the potential for bioconcentration of THF in aquatic organisms is low (PubChem 2019f).

7.9.2.8.2 Ecotoxicity

No data were found for toxicity in green algae. The ECOSAR model (EPA 2018) predicts a 96-hour EC_{50} of 136mg/L in green algae.

The LC_{50} in *Daphnia* is reported to be 5930 mg/L and >10,000 mg/L for a 24-hour exposure, and the LC_{50} in various species of fish ranges from 2400 mg/L to 5900 mg/L for a 48-hour exposure. The 96-hour LC_{50} in fathead minnow (*Pimephelas promelas*) is 2160 mg/L (PubChem 2019f).

7.9.2.8.3 Degradation/Treatment

Hydrolysis is not expected to be an important environmental fate process since THF lacks functional groups that hydrolyze under environmental conditions. Vapor-phase THF will be degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals and nitrate ions; the half-lives of these two reactions in air are 21–24 hours and 3 days, respectively (PubChem 2019f).

THF is rapidly degraded by aerobic biodegradation. Using the European Economic Community manometric repirometric method in 22 different laboratories, THF reached a mean of 34% of

theoretical BOD within 28 days. THF is resistant to anaerobic biodegradation. With a primary digesting sludge as an innoculum, the lag period was more than 60 days (HSDB 2011).

7.10 p-Toluenesulfonic acid [PTSA]

7.10.1 General Information

Anhydrous PTSA is a crystalline solid (Budavari 1996). The IUPAC nomenclature is 4-methylbenzenesulfonic acid (PubChem 2019g). Figure 7 illustrates the molecular structure of PTSA.

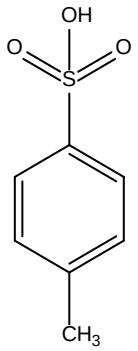

Figure 7. PTSA

7.10.2 Toxicology Data

The primary hazard of PTSA arises from its high acidity.

7.10.2.1 Oral

The acute oral LD_{50} of PTSA is reported to be 1410 mg/kg in the rat, 735 mg/kg in mice, and >316 mg/kg in quail (PubChem 2019g).

No chronic LOAEL data were available. TOPKAT modeling predicts a chronic LOAEL of 60.3 mg/kg-day at high confidence.

7.10.2.2 Inhalation

PTSA may cause respiratory irritation (PubChem 2019g).

No experimental data were found. TOPKAT modeling predicts an acute inhalation LC_{50} in rats of >10 g/m^3-hour at high confidence.

7.10.2.3 Dermal

PTSA may cause skin irritation or corrosion (PubChem 2019g).

7.10.2.4 Ocular

PTSA may cause irritation or serious eye damage (PubChem 2019g).

7.10.2.5 Development and Reproduction

No experimental data were found. TOPKAT modeling predicts PTSA will be a developmental or reproductive toxicant at high confidence.

7.10.2.6 Neurotoxicity

No experimental data were found.

7.10.2.7 Genotoxicity

No experimental data were found. TOPKAT modeling predicts PTSA will not be mutagenic in the Ames assay.

7.10.2.8 Carcinogenesis

No experimental data were found. TOPKAT modeling predicts PTSA will not be carcinogenic.

7.10.2.9 Ecotoxicology

7.10.2.9.1 Fate and Transport

PTSA is a strong acid and is completely dissociated and highly soluble in water. It is expected to be highly mobile and may pose a hazard to surface and drinking water. PTSA will volatilize from both water and wet surfaces and is expected to exist in the atmosphere as both a vapor and a particulate. PTSA will not bioaccumulate in aquatic organisms (HSDB 1995).

7.10.2.9.2 Ecotoxicity

No experimental data were found. The ECOSAR (2018) program predicts a 96-hour EC_{50} of 3.88×10^4 mg/L in green algae, a 48-hour LC_{50} of 1.42×10^5 mg/L in *Daphnia,* a 96-hour LC_{50} of 3.17×10^5 mg/L in fish, and a 14-day LC_{50} of 5.59×10^3 mg/L in earthworms.

7.10.2.9.3 Degradation/Treatment

Vapor phase PTSA will react with photochemically-produced hydroxyl radicals with an estimated half-life of 11.8 days. Biodegradation may proceed very slowly if acclimated microorganisms are absent from the bodies of water (HSDB 1995).

8 Discussion

8.1 Compound Summaries

8.1.1 2-Mercaptobenzothiazole

Dermal exposure appears to be the most significant hazard of 2-MBT, both occupationally and from exposure to rubber products. Although the oral and inhalation toxicities of 2-MBT are high, they are considered low-impact since exposure by ingestion or inhalation is considered unlikely, and there is no epidemiological evidence for toxicity via these routes. Genotoxicity is not significant, but there is some evidence of potential carcinogenicity in long-term rodent studies, and 2-MBT is considered a possible human carcinogen (bladder cancer).

Ecotoxicity is reported to be significant, but measured toxicity values do not reflect this. Environmental persistence is expected to be high, with possible adverse effects on bacteria that biodegrade xenobiotics.

8.1.2 Melamine

Accumulation of melamine crystals within the bladder and kidney represents the greatest hazard to animal species. Frank melamine toxicity is relatively low by regular routes of exposure: oral, inhalation and dermal. Occupational hazards are low although melamine is a mild ocular irritant. There are indications that melamine may be a neurological hazard during development, but this is not relevant to adults. Melamine does not represent a genotoxic or carcinogenicity hazard.

High water solubility means melamine will be highly mobile in groundwater. Based on ECOSAR (2018) modeling predictions, melamine is predicted to be low in direct toxicity towards aquatic species.

8.1.3 Formaldehyde

Formaldehyde is considered a probable human carcinogen. Formaldehyde is an acute oral and inhalation hazard, an ocular and dermal irritant, and a likely dermal sensitizer. Developmental and reproductive effects are minimal, and some mild neurological impairment has been noted upon chronic exposure. Health effects of formaldehyde might be mitigated by its extreme reactivity, shortening potential exposures.

Ecotoxicology hazards are moderate overall. Formaldehyde’s high reactivity will reduce environmental exposures.

8.1.4 Pentaerythritol tetrakis (3-mercaptopropionate)

PTT is moderately toxic via ingestion and probably inhalation, and non-toxic dermally. Occupational exposure hazards are low to moderate, with skin sensitization a possible hazard. PTT is anticipated to be only a mild ocular irritant and is not expected to be genotoxic or carcinogenic. Developmental or reproductive toxicity is possible, but predictions are low-confidence.

Lack of environmental mobility limits environmental toxicity. If discharged directly to water, PTT is expected to pose a hazard to organisms at lower trophic levels. Persistence in the environment is expected to be weeks to months.

8.1.5 Sodium dodecyl sulfate

SDS is a relatively non-toxic surfactactant found in many cleaning solutions. In pure form, it is moderately toxic by ingestion or inhalation, and non-toxic dermally. SDS poses a moderate occupational hazard due to dermal and ocular irritation. It is not genotoxic or carcinogenic, and it is not known to be a developmental or reproductive toxicant or a neurological hazard.

SDS is not mobile in the environment; it is moderately toxic toward aquatic species. SDS is susceptible to degradation by aerobic bacteria with a relatively short biological half-life.

8.1.6 Gum arabic

Gum arabic is a non-toxic natural product. Historical use in printing processes led to cases of "printers asthma," but other products that have since been substituted have eliminated this problem (HSDB 2002).

8.1.7 Tetrahydrofuran

THF is a severe ocular hazard, causing both irritation and corrosion depending upon the concentration. THF is moderately toxic via the oral route of exposure. By inhalation and dermal exposure, toxicity is low although dermal irritation and drying are possible. Mutagenicity testing is negative, and the compound is not classified as a human carcinogen.

High solubility and mobility make THF a groundwater transport hazard, but its toxicity toward wildlife species is relatively low. Environmental persistence is moderate.

8.1.8 p-Toluenesulfonic acid

PTSA is a highly soluble, strong acid. Its most significant hazard is to eyes, where it is classified as a strong irritant/corrosive. QSAR modeling indicates possible developmental or reproductive toxicity. Frank toxicity is low to moderate; inhalation and dermal toxicity are essentially nil, and oral toxicity is moderate. PTSA is not believed to be either mutagenic or carcinogenic.

Ecotoxicity is low, but mobility in water is very high. PTSA will not bioaccumulate, and it is biodegradable by aerobic microorganisms.

8.2 Regulations and Standards

8.2.1 2-Mercaptobenzothiazole

The European Commission has set a Threshold Limit Value (TLV) of 3 mg/m^3 for 2-MBT respirable particulates and 10 mg/m^3 for inhalable 2-MBT particulates (PubChem 2019a).

A workplace environment exposure limit for an 8-hour exposure has been established at 5 mg/m^3 on the basis of dermal sensitization (PubChem 2019a).

8.2.2 Melamine

Melamine is considered of low relative toxicity except by direct ingestion, and it is approved by the U.S. Food and Drug Administration (FDA) as an indirect food additive derived from packaging materials. The estimated level of melamine in food resulting from approved uses is less than 15 µg/kg (0.015 ppm) (FDA 2018, HSDB 2012).

In the aftermath of the pet food and infant formula crises, the FDA issued an Interim Safety and Risk Assessment of Melamine and its Analogues in Food for Humans. This Interim Assessment was based upon the 13-week rat study by Melnick et al. (1984), and applied uncertainty factors for interspecies variability, extrapolating from a LOAEL to a NOAEL, and uncertainty surrounding the presence of melamine analogues, especially cyanuric acid, which affect the formation of urinary crystals, for a combined uncertainty factor of 1000. The maximum tolerated dose for humans older than 3 years of age was calculated to be 0.63 mg/kg-day. Applying assumptions about the weight of the average human and the mass of food consumed daily, this resulted in a Maximum Contaminant Level of 2.5 ppm or 2.5 mg/kg in food. The FDA was unable to establish a safe level of consumption for infants and toddlers (FDA 2012).

Only a month after issuing the Interim Safety and Risk Assessment of Melamine and its Analogues in Food for Humans, the FDA updated the assessment to include infants because analysis of infant formula samples had revealed that the presence of both melamine and cyanuric acid at the same time, a complicating issue for the first assessment, was found to be uncommon. Accordingly, FDA applied a 10-fold uncertainty factor for infants, but removed the 10-fold factor for presence of multiple analogues. Hence, a Tolerated Daily Ingestion (TDI) level of 0.063 mg/kg-day was set for infants. Applying assumptions about the weight of infants and the quantity of formula consumed daily, a Maximum Contaminant Level of 1.0 ppm melamine in food was established (FDA 2008b).

8.2.3 Formaldehyde

The NIOSH 15-minute Recommended Exposure Limit (REL) is a time-weighted 0.016 ppm, and the OSHA Permissible Exposure Limit (PEL) is a time-weighted 0.75 ppm with a short-term exposure limit of 2 ppm (1 ppm = 1.23 mg/m^3)(NIOSH 2018).

The ACGIH has established a TLV of 0.3 ppm based upon sensitization (PubChem 2019c).

The EPA has established a Federal drinking water guideline of 1000 µg/L. Several states have established more stringent standards, including California, New Jersey, and New Hampshire (100 µg/L), Florida (600 µg/L), and Maine (140 µg/L). Wisconsin and Minnesota enforce at the level of the Federal standard (PubChem 2019c).

The ATSDR has established a chronic inhalation Minimal Risk Level (MRL) of 0.008 ppm (0.010 mg/m^3) based on respiratory effects in humans, and a chronic oral MRL of 0.2 mg/kg-day. The

MRL is an estimate of the daily human exposure that is likely to be without appreciable risk of adverse non-cancer health effects over a lifetime (ATSDR 2010b).

The Reference Dose (RfD) for formaldehyde is 0.2 mg/kg-day based on decreased body weight gain and effects on the stomach in rats (PubChem 2019c).

8.2.4 Pentaerythritol tetrakis(3-mercaptopropionate)

No regulations or standards pertaining to PTT were found.

8.2.5 Sodium dodecyl sulfate

No regulations or standards pertaining to SDS were found.

8.2.6 Gum arabic

Gum arabic is GRAS when used in accordance with accepted practices (HSDB 2002).

8.2.7 Tetrahydrofuran

For THF, OSHA has established a PEL of 200 ppm (590 mg/m^3) as an 8-hour time-weighted average (TWA). The NIOSH REL is 200 ppm for a 10-hour exposure, and a 15-minute Short-Term Exposure Limit (STEL) of 250 ppm (735 mg/m^3). The Immediately Dangerous to Life or Health (IDLH) level is 2000 ppm (PubChem 2019).

Based on skin considerations, the ACGIH has set an 8-hour TWA TLV of 50 ppm, and a 15-min STEL of 100 ppm (PubChem 2019).

Several states have adopted drinking water guidelines for THF: Massachusetts (600 µg/L), New Hampshire (150 µg/L), Maine (70 µg/L), Wisconsin (50 µg/L), and Florida (4.6 µg/L) (PubChem 2019f).

8.2.8 p-Toluenesulfonic acid

No regulations or standards pertaining to PTSA were found.

8.3 Conclusions

A cancer hazard is associated with 2-MBT and formaldehyde. While there are data gaps for some of the other compounds in this formulation, most of the hazard is derived from typical occupational concerns, such as dermal and ocular irritation, that are normally addressed via PPE. There are additional issues for some compounds, but there are factors in mitigation. For example, while 2-MBT is classified as highly toxic, it is widely used in industrial rubber products, and there is no epidemiological evidence of serious health issues in humans although workers have been found to be at increased risk of bladder cancer. Formaldehyde represents a potential concern, as it is a likely human carcinogen and also poses hazard for inhalation, oral, and

dermal exposures and moderate dermal, ocular, and neurological effects. The remaining compounds in the formulation are of low to moderate toxicity and are not thought to be a serious exposure concern.

9 Recommendations

Measures should be taken to address some of the data gaps outlined in this report via experimental work, although none of these factors appear critical to acceptance of this formulation. Notably, there is a question regarding the acute oral toxicity of 2-MBT in rats: the value of 100 mg/kg has been reported but is unverified. Little publicly documented experimental information is available for PTT. This shortfall could be addressed as time and resources permit, but is not critical to the current project. There are no significant information shortfalls for the remaining compounds in the formulation.

10 Point of Contact

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Toxicology Report No. S.0058900.3-18, March 2018–April 2019

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Appendix A

References

An, L. and W. Sun. 2017. A Brief Review of Neurotoxicity Induced by Melamine. *Neurotox Res,* 32:301–9.

Atkinson, R. and J. Arey. 2003. Atmospheric degradation of volatile organic compounds. *Chem Rev,* 103:4605–38.

ATSDR. 1999. *Toxicological Profile for Formaldehyde;* accessed 15 March 2019. https://www.atsdr.cdc.gov/ToxProfiles/

ATSDR. 2010. *Addendum to the Toxicological Profile for Formaldehyde;* accessed 15 March 2019. https://www.atsdr.cdc.gov/ToxProfiles/

BIOVIA. 2015. Toxicity Prediction Komputer Assisted Technology (TOPKAT), Dassault Systems. San Diego, California.

Brewster, D.W., K.J. Mirly, A.G. Wilson, and J.W. Barnett, Jr. 1989. Lack of in vivo DNA binding of mercaptobenzothiazole to selected tissues of the rat. *Biochem Biophys Res Comm,* 165:342–48.

Brown, C.A., K.-S. Jeong, R.H. Poppenga, B. Puschner, D.M. Miller, A.E. Ellis, K.-I. Kang, S. Sum, A.M. Cistola, and S.A. Brown. Outbreaks of renal failure associated with melamine and cyanuric acid in dogs and cats in 2004 and 2007. *J Vet Diagn Invest,* 19(5):525–31.

Budavari, S. 1996.*The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals, 12th Ed*., Whitehouse Station, New Jersey: Merck & Co., Inc.

ChemIDPlus. 2019. *Pentaerythrityl tetrakis(3-mercaptopropionate).* TOXNET; accessed 18 March 2019. https://toxnet.nlm.nih.gov/

CPDB. 2007. *Melamine;* accessed 8 July 2009. http://potency.berkeley.edu/chempages/MELAMINE.html

Cruywagen, C.W., M.A. Stander, M. Adonis, and T. Calitz. 2009. Hot topic: pathway confirmed for the transmission of melamine from feed to cow's milk [Abstract]. *J Dairy Sci,* 92(5):2046.

DeWever, H., S. Van den Nest, and H. Verachtert. 1998. Inhibitory effects of 2-mercaptobenzothiazole on microbial growth in a variety of trophic conditions. *Environ Toxicol Chem,* 16:843–48.

EPA. 2019. ECOTOX Knowledgebase; accessed 18 March 2019. https://cfpub.epa.gov/ecotox

EPA. 2018. ECOSAR Version 2.0. Washington, DC.

EPA. 2015a. EPI Suite 4.11. Washington, DC.

EPA. 2015b. ECOSAR Version 1.11. Washington, DC.

EPA. 2008. EPI Suite 4.11. Washington, DC.

European Chemicals Board (now Agency) (ECB). 2007. *IUCLID 6 Dataset,* Melamine (CAS# 108-78-1), 75; accessed 14 May 2019. https://iuclid6.echa.europa.eu/get-reference-substances

FDA 2018. *Melamine Pet Food Recall—Frequently Asked Questions;* accessed 8 March 2019. https://www.fda.gov/AnimalVeterinary/SafetyHealth/RecallsWithdrawals/ucm129932.htm

Gonzalez, J., B. Puschner, V. Perez, M.C. Ferreras, L. Delgado, M. Munoz, C. Perez, et al. 2009. Nephrotoxicosis in Iberian piglets subsequent to exposure to melamin and derivatives in Spain between 2003 and 2006. *J Vet Diagn Invest,* 21(4):558–63.

HSDB. 2015. *2-Mercaptobenzothiazole*. TOXNET; accessed 5 March 2019. https://toxnet.nlm.nih.gov/

HSDB. 2012. *Melamine*. TOXNET; accessed 8 March 2019. https://toxnet.nlm.nih.gov/

HSDB. 2011. *Tetrahydrofuran*. TOXNET; accessed 22 March 2019. https://toxnet.nlm.nih.gov/

HSDB. 2002. *p-Toluenesulfonic acid.* TOXNET; accessed 26 March 2019. https://toxnet.nlm.nih.gov/

HSDB. 2002. *Acacia*. TOXNET; accessed 21 March 2019. https://toxnet.nlm.nih.gov/

HSDB. 2000. *Dodecyl sulfate.* TOXNET; accessed 20 March 2019. https://toxnet.nlm.nih.gov/

HSDB. 1995. *p-Toluenesulfonic acid*. TOXNET; accessed 25 March 2019. https://toxnet.nlm.nih.gov/

IARC. 1986. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man, Vol. 39, *Some Chemicals Used in Plastics and Elastomers*, Geneva: WHO.

Lan, Q., M.T. Smith, X. Tang, W. Guo, R. Vermeulen, Z. Ji, W. Hu, et al. 2015. Chromosome-wide aneuploidy study of cultured circulating myeloid progenitor cells from workers occupationally exposed to formaldehyde. *Carcinogenesis,* 36:160–67.

Mast, T.J., R.J. Weigel, R.B. Westerberg, B.A. Schwetz, and R.E. Morrissey. 1992. Evaluation of the potential for developmental toxicity in rats and mice following inhalation exposure to tetrahydrofuran. *Fundam Appl Toxicol,*18:255–65.

McGregor, D.B., A. Brown, P. Cattanach, I. Edwards, D. McBride, C. Riach, and W.J. Caspary. 1988. Responses of the L5178Y tk+/tk- mouse lymphoma cell forward mutation assay. *Environ Mol Mutagen,* 12(1):85–154.

Melnick, R.L., G.A. Boorman, J.K. Haseman, R.J. Montali, and J. Huff. 1984. Urolithiasis and bladder carcinogenicity of melamine in rodents. *Toxicol Appl Pharmacol,* 72(2):292–303.

NIOSH. 2018. Formaldehyde. *NIOSH Pocket Guide to Chemical Hazards.* Centers for Disease Control and Prevention; accessed 13 March 2019. https://www.cdc.gov/niosh/npg/npgd0293.html

NIOSH. 2018. Tetrahydrofuran. *NIOSH Pocket Guide to Chemical Hazards.* Centers for Disease Control and Prevention; accessed 22 March 2019. https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr475.pdf

NTP. 1988. Technical Report Series, No. 332, *Toxicology and Carcinogenesis Studies of 2-Mercaptobenzothiazole (CAS No. 149-30-4) in F344/N and B6C3F1 Mice (Gavage Studies).* https://ntp.niehs.nih.giv/ntp/htdocs/lt_rpts/tr332.pdf

NTP. 1983. Toxicology and Carcinogenesis Studies of Melamine (CAS No. 108-78-1) in F344/N Rats and B6C3F1 Mice (Feed Studies). *Natl Toxicol Program Tech Rep Ser,* 245:1–171.

NTP. 1982. Carcinogenesis Bioassay of Gum Arabic (CAS No. 9000-01-5) in F344 Rats and B6C3F1 Mice (Feed Study). *Natl Toxicol Program Tech Rep Ser,* 227:1–124; accessed 21 March 2019. https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr227.pdf

Obe, G. and B. Beek. 1979. Mutagenic activity of aldehydes. *Drug Alcohol Depend,* 4:91–4.

OECD. 1999. *Screening Information Data Set for Melamine, CAS # 108-78-1,* 168–169; accessed 14 May 2019. http://www.inchem.org/documents/sids/sids/108781.pdf

OSHA. 2012. *The Globally Harmonized System of Classification and Labeling of Chemicals;* accessed 17 November 2012. http://www.osha.gov/dsg/hazcom/ghs.html

PubChem. 2019a. *2-Mercaptobenzothiazole;* accessed 12 March 2019. https://pubchem.ncbi.hlm.nih.gov/

PubChem. 2019b. *Melamine;* accessed 8 March 2019. https://pubchem.ncbi.nlm.nih.gov/

PubChem. 2019c. *Formaldehyde;* accessed 12 March 2019. https://pubchem.ncbi.nlm.nih.gov/

PubChem. 2019d. *Propanoic acid, 3-mercapto-, 1,1'-(2,2-bis((3-mercapto-1-oxopropoxy)methyl)-1,3-propanediyl) ester;* accessed 12 March 2019. https://pubchem.ncbi.nlm.nih.gov/

PubChem. 2019d. *Sodium lauryl sulfate;* accessed 15 March 2019. https://pubchem.ncbi.nlm.nih.gov/

PubChem. 2019e. *Tetrahydrofuran;* accessed 21 March 2019. https://pubchem.nlm.nih.gov/

PubChem. 2019f. *4-Methylbenzenesulfonic acid;* accessed 25 March 2019. https://pubchem.ncbi.nlm.nih.gov/

Ramusino, M.C. and A. Tenconi. 1980. Melamine action on *Biomphalaria glabrata say* (mollusca, gasteropoda). *Riv Biol,* 73(4):588–91 [Italian].

Ramusino, M.C. and G. Vailati. 1982. Modifications in *Salmo gairdneri* due to 2,4,6- triamino-1,3,5-triazine (melamine). *Acta Embryol Morphol Exp,* 3(1):41–8 [Italian].

Reimschuessel, R., C.M. Gieseker, R.A. Miller, J. Ward, J. Boehmer, N. Rummel, D.N. Heller, et al. 2008. Evaluation of the renal effects of experimental feeding of melamine and cyanuric acid to fish and pigs. *Am J Vet Med,* 69(9):1217–28.

Rodwell, D.E., J.M. Gerhart, E.C. Bisinger, M.D. Mercieca, and J.J. McKenzie. 1990. Developmental toxicity study of 2-mercaptobenzothiazole (MBT) in two species [Abstract]. *Teratology,* 41:587.

Sigma-Aldrich. 2018. *Sodium dodecyl sulfate;* accessed 20 March 2019. https://www.sigmaaldrich.com/safety-center.html

Sigma-Aldrich. 2014. *Pentaerythritol tetrakis(3-mercaptopropionate);* accessed 18 March 2019. https://www.sigmaaldrich.com/safety-center.html

Trochimowicz, H.J., G. L. Kennedy, and N.D. Krivanek. 2001. Alkylpyridines and Miscellaneous Organic Nitrogen Compounds. In: Bingham, E., B. Cohrssen, and C.H. Powell, eds. *Patty's Toxicology*, *5th Ed., Vol. 4: Hydrocarbons and Organic Nitrogen Compounds,* 1334–37. New York: John Wiley & Sons.

Werawattanachai, N., P. Towiwat, S. Unchern, and T.J. Maher. 2007. Neuropharmacological profile of tetrahydrofuran in mice. *Life Sci,* 80:1656–63.

Whittaker, M.H., A.M. Gebhart, T.C. Miller, and F. Hammer. 2004. Human health risk assessment of 2-mercaptobenzothiazole in drinking water. *Toxicol Ind Health,* 20:149–63.

Appendix B

Globally Harmonized System

"GHS" is the acronym for the Globally Harmonized System of Classification and Labeling of Chemicals. The GHS attempts to establish international consensus for defining health, physical, and environmental hazards of chemicals; creates a classification process for comparison with defined hazard criteria; and communicates hazard information and protective measures on labels and Safety Data Sheets (formerly known as Material Safety Data Sheets). The GHS attempts to reduce differences among levels of worker protection established by the different countries and reduce regulatory burden and barriers to commerce while establishing consistent standards for classification. The GHS is the result of an international mandate adopted in the 1992 United Conference on Environment and Development, often called the "Earth Summit." The harmonization and classification of chemicals was one of six program areas endorsed by the United Nations General Assembly to strengthen international efforts in the environmentally sound management of chemicals.

While the GHS comprises several aspects, the most important area for our purposes is classification of chemicals into various hazard categories based upon their effects and the route of exposure. Tables B-1 through B-4 present tabular extracts of the criteria for acute toxicity (both oral and inhalation), skin corrosion/irritation, ocular effects, and aquatic toxicity (both acute and chronic), respectively. More information can be found in the original source material (OSHA 2012).

Table B-1. GHS Acute Toxicity

	Category 1	Category 2	Category 3	Category 4	Category 5
Oral (mg/kg)	≤5	>5 ≤50	>50 ≤300	>300 ≤2000	Criteria: –Anticipated LD50 between 2000 and 5000 mg/kg –Indication of significant effects in humans. –Any mortality in Category 4 –Significant clinical signs in Category 4 –Indications from other studies. *If assignment to a more hazardous class is not warranted.
Dermal (mg/kg)	≤50	>50 ≤200	>200 ≤1000	>1000 ≤2000	
Gases (ppm)	≤100	>100 ≤500	>500 ≤2500	>2500 ≤5000	
Vapors (mg/L)	≤0.5	>0.5 ≤2.0	>2.0 ≤10	>10 ≤20	
Dusts & Mists (mg/L)	≤0.05	>0.05 ≤0.5	>0.5 ≤1.0	>1.0 ≤5	

Legend:
mg/kg = milligrams per kilogram
mg/L = millgrams per liter
ppm = parts per million

Table B-2. GHS Skin Corrosion/Irritation

<table>
<tr><th colspan="3">Skin Corrosion
Category 1</th><th>Skin Irritation
Category 2</th><th>Mild Skin Irritation
Category 3</th></tr>
<tr><td colspan="3">Destruction of dermal tissue; visible necrosis in at least one animal.</td><td rowspan="2">Reversible adverse effects in dermal tissue
Draize score: ≥ 2.3, <4.0, or persistent inflammation</td><td rowspan="2">Reversible adverse effects in dermal tissue

Draize score: ≥ 1.5, <2.3</td></tr>
<tr><td>Subcategory 1A
Exposure < 3 minutes
Observation < 1 hour</td><td>Subcategory 1B
Exposure < 1 hour
Observation < 14 days</td><td>Subcategory 1C
Exposure < 4 hours
Observation < 14 days</td></tr>
</table>

Table B-3. GHS Eye Effects

<table>
<tr><th>Category 1: Serious Eye Damage</th><th colspan="2">Category 2: Eye Irritation</th></tr>
<tr><td rowspan="2">Irreversible damage 21 days after exposure

Draize score:
Corneal opacity ≥ 3
Iritis ≥ 1.5</td><td colspan="2">Reversible adverse effects on cornea, iris, conjunctiva

Draize score:
Corneal opacity ≥ 1
Iritis > 1
Redness ≥ 2
Chemosis ≥ 2</td></tr>
<tr><td>Irritant
Subcategory 2A
Reversible in 21 days</td><td>Mild irritant
Subcategory 2B
Reversible in 7 days</td></tr>
</table>

Table B-4. GHS Acute and Chronic Aquatic Toxicity

<table>
<tr><th>Acute Category I
Acute toxicity ≤ 1.00 mg/L</th><th>Acute Category II
Acute toxicity > 1.00 but ≤10.0 mg/L</th><th colspan="2">Acute Category III
Acute toxicity > 10.0 but < 100 mg/L</th></tr>
<tr><td>Chronic Category I
Acute toxicity ≤ 1.00 mg/L and lack of rapid biodegradability and log Kow ≥ 4, unless BCF < 500.</td><td>Chronic Category II
Acute toxicity > 1.00 mg/L but ≤ 10.0 mg/L and lack of rapid biodegradability, and log Kow ≥ 4, unless BCF < 500 and unless chronic toxicity > 1 mg/L.</td><td>Chronic Category III
Acute toxicity > 10.0 mg/L but ≤ 100.0 mg/L and lack of rapid biodegradability and log Kow ≥ 4, unless BCF < 500 and unless chronic toxicity > 1 mg/L.</td><td>Chronic Category IV
Acute toxicity > 100.0 mg/L and lack of rapid biodegradability and log Kow ≥ 4, unless BCF < 500 and unless chronic toxicity > 1 mg/L.</td></tr>
</table>

Legend:
BCF = bioconcentration factor
mg/L = milligrams per liter

Glossary
Acronyms and Abbreviations

2-MBT	2-Mercaptobenzothiazole
ACGIH	American Conference of Governmental Industrial Hygienists
APHC	U.S. Army Public Health Center
atm-m^3/mol	unit of Henry's Law constant
ATSDR	Agency for Toxic Substances Disease Registry
BCF	bioconcentration factor
BOD	Biological Oxygen Demand
bp	boiling point
°C	degrees Celsius
CAS RN	Chemical Abstracts Service Registry Number
CHO	Chinese hamster ovary
CNS	central nervous system
CPDB	Carcinogenic Potency Database
Cr(VI)	hexavalent chromium
DNA	deoxyribonucleic acid
DOD	Department of Defense
DTIC	Defense Technical Information Center
EC_{50}	effective concentration to achieve 50-percent effect
ECB	European Chemicals Board
ECOSAR	Ecological Structure Activity Relationships
ECOTOX	ECOTOXicology Database System
EPA	U.S. Environmental Protection Agency
EPI	Estimation Programs Interface Suite for Microsoft Windows
ESOH	environment, safety, and occupational health
FDA	U.S. Food and Drug Administration
GD	gestation day
GHS	Globally Harmonized System
g/kg	grams per kilogram

g/m^3	grams per cubic meter
g/mol	grams per mol
GRAS	generally recognized as safe
HSDB	Hazardous Substances Data Bank
IARC	International Agency for Research on Cancer
IC_{50}	concentration causing 50-percent inhibition
IUPAC	International Union of Pure and Applied Chemistry
K_H	Henry's Law constant
K_{OC}	organic carbon-normalized sorption coefficient for soil and sediment
LC_{50}	concentration resulting in 50% mortality
LC_{LO}	lowest lethal concentration
LD_{50}	dose resulting in 50% mortality
LOAEL	lowest observed adverse effect level
log K_{OC}	organic carbon partition coefficient
log K_{ow}	octanol-water partition coefficient
MCL	Maximum Contaminant Level
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
mg/m^3	milligrams per cubic meter
mmHg	millimeters Mercury
MRL	Minimal Risk Level
MW	molecular weight
µg/mL	micrograms per milliliter
n/a	not applicable
ND	no data
NIOSH	National Institute for Operational Safety and Health
nm	nanometer
NOAEL	no observed adverse effect level
NTP	National Toxicology Program
OECD	Office of Economic Cooperation and Development
OSHA	Occupational Safety and Health Administration

PPE	personal protective equipment
ppm	parts per million
PTSA	p-Toluenesulfonic acid
PTT	pentaerythrytol tetrakis(3-mercaptopropionate)
RDT&E	research, development, testing, and evaluation
REL	Recommended Exposure Limit
SDS	sodium dodecyl sulfate
SERDP	Strategic Environmental Research and Development Program
STEL	Short-term Exposure Limit
TAC	Total Allowable Concentration
THF	tetrahydrofuran
TLV	Threshold Limit Value
TOPKAT	Toxicity Prediction Komputer Assisted Technology
TOXNET	Toxicology Data Network
TWA	time-weighted average
vp	vapor pressure
WHO	World Health Organization