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Literature Review

Health Effects for Chemicals in 2014 West Virginia Chemical Release: Crude MCHM Compounds, PPH and DiPPH

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GLOSSARY OF TERMS

ACToR	USEPA's Aggregated Computational Toxicology Resource
BOD	Biochemical oxygen demand (sometimes (incorrectly) "biological" oxygen demand)
BW	Body weight
CAS	Chemical Abstract Service
CAS number	Unique identifier for a chemical (Warning: Chemicals are sometimes mislabeled in the literature with respect to CAS number, the CAS number may be incorrectly assigned to a structure)
CDC	Centers for Disease Control and Prevention
CHDM	1,4-Cyclohexanedimethanol (CAS 105-08-8) (common usage)
CO_2	Carbon dioxide
COD	Chemical oxygen demand
Crude MCHM	Mixture of chemicals containing MCHM as the major component
DiPPH	Dipropylene glycol phenyl ether (CAS 51730-94-0) (common usage)
DMCHDC	1,4-Dimethyl cyclohexanedicarbonate (CAS 94-60-0) (this study)
DW Advisory Level	Drinking Water Advisory Level
EC50	Effective concentration for 50% response
LC_{50}	Lethal concentration for 50% mortality
LD_{50} Lethal dose	Lethal dose for 50% mortality
LOAEL	Lowest-observed-adverse-effect level
MCHM	Pure 4-methyl-1-cyclohexanemethanol (CAS 34885-03-5) (common usage). (Note: "MCHM" will indicated the pure MCHM compound, while "Crude MCHM" is the mixture of MCHM and other compounds described elsewhere.)
MeOH	Methanol (CAS 67-56-1) (common usage)
MMCHC	Methyl 4-methylcyclohexane-1-carboxylate (CAS 51181-40-9) (this study)
MMCHM	4-(Methoxymethyl) cyclohexane methanol (CAS 98955-27-2) (this study)
MSDS	Material Safety Data Sheet
NLM	US National Library of Medicine
NOAEL	No-observed-adverse-effect level
NOEC	No Observed Effect Concentration
NOEL	No Observed Effect Level
OECD	Organization for Economic Development
PPH	Propylene glycol phenyl ether (CAS 770-35-4)

Q&A	Question and answer
SIDS	Screening Information Data Set
Screening Level	Directly equated by CDC to DW Advisory (CDC, 2014c)
TOXNET	Toxicology Data Network (US National Library of Medicine (NLM))
UF	Uncertainty factor
USEPA	United States Environmental Protection Agency
WV	West Virginia

NOTE ON HYPERLINKS

To facilitate ease of tracking references for the reader of this document, hyperlinks were established at the point of reference throughout the document. As a disclaim er, it must be stated that the material referenced was based on the content of the hyperlinked webpage on Mar 1 to 3, 2014, and that the link may have changed or disappeared after that date.

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1.0 BACKGROUND

On January 9, 2014, a chemical storage tank owned by Freedom Industries , Inc. leaked approximately 10,000 gallons of a mixture of Crude MCHM and Stripped PPH into the Elk River, West Virginia. The spilled liquid was transported downriver and was withdrawn into the West Virginia American Water treatment plant intake. This water treatment plant serves approximately 300,000 people located in nine counties in southwestern West Virginia. Contaminated water passed through the water treatment facility and was pumped into the water distribution system. Reports of licorice odors at home owner taps and hospital admittances were signs that the population had contacted the contaminated tap water. The cause of the chemical spill appears to have been related to the failure of both the storage tank containing the chemical mixture and the failure of a containment wall (Eastman 2014a). The February 27, 2014 Eastman document replaced the original February 7, 2014 document.

Today, the exact chemical composition of the spilled liquid and what reached the drinking water taps of affected residents remains somewhat undefined. Initial reports disclosed the leak of Crude MCHM, which contains a mixture of six different organic compounds. Later reports by Freedom Industries disclosed the tank that leaked also contained PPH Glycol Ether (PPH). The statement by Freedom Industries stated that the tank contained 88.5% CrudeMCHM, 7.3% PPH (CAS 770-35-4) and 4.2% water. A furtherreport stated that in fact the tank also contained a third mixture, DiPPH as well. The exact composition however has not been chemically confirmed. The apparent source of the PPH was in a mixture called PPH Stripped (Freedom, 2013). DOW Chemical states that they do not produce nor sell Stripped PPH, did not sell PPH directly to Freedom Industries, and suggested contact with Freedom Industries directly to determine their supplier (DOW, 2014).

1.1 Advisory Level Terminology

Various exposure routes are possible for drinking water contaminants including ingestion, inhalation (e.g., during a shower), dermal uptake (e.g., during bathing), and other routes. Estimates of the relative contribution of these routes has not been documented in the literature for the study compounds.

Furthermore, tap water temperatures and air ventilation conditions within buildings are important factors to consider when examining chemical exposure potential. According to water quality monitoring results obtained by a January, 2014, in a study by Whelton and colleagues (2014) , and again more recently by the WVTAP team, residential tap water temperatures in the study area of West Virginia ranged from 4 °C to 60 °C. Discussions with the West Virginia Army National Guard also revealed that industrial dishwashers at schools can reach temperatures of 140 °C to 160 °C (Whelton, 2014). Water temperature may play a key role in inhalation exposure because chemicals tend to become m ore volatile from water at higher temperatures (due to increasing Henry's Law constant). Temperature may play other important roles, as well, including faster reactions with oxidants (e.g., chlorine and permanganate) in the drinking water. Another factor r elated to chemical exposure potential is the effectiveness of air ventilation systems in houses in bathrooms and kitchens. For example, within homes visited in West Virginia by Whelton's team (2014), and the more recent WVTAP team, air ventilation varied significantly. During these investigations, some bathroom vent fans were found inoperable and some bathroom windows could not be opened because of mechanical problems. These non-ideal conditions influence the air exchange rate and, hence, potentially the co ncentration of any volatilized chemicals (Whelton, 2014). Consideration in detail of

various exposure routes including drinking water ingestion, inhalation and dermal exposure is a relevant topic to be considered by the expert toxicology panel which will convene in late March or early April, 2014.

Various terms are used to describe the significance of chemical concentrations in drinking water. For regulatory purposes, maximum contaminant levels (MCL) are used by the USEPA, specifically (USEPA 2012): ""The highest level of a contaminant that is allowed in drinking water. MCLs are set as close to the MCLG as feasible using the best available analytical and treatment technologies and taking cost into consideration. MCLs are enforceable standards." Maximum Contaminant Level Goal (MCLG) is related is a non-enforceable health benchmark goal "...at which no known or anticipated adverse effect on the health of persons is expected to occur and which allows an adequate margin of safety." There are numerous chemicals that have established drinking water MCLs. None of the known chemical ingredients of Crude MCHM or Stripped PPH however have MCLs.

During the Freedom Industries chemical spill response, the Centers for Disease Control and Prevention (CDC) (CDC, 2014a) and West Virginia Governor Tomblin (Tomblin, 2014a) used the term "screening level". The term "screening level" is non-standard terminology for drinking water. For example, the term "screening level" is not used in the Drinking Water Advisory Communication Toolbox (CDC, 2013) put out jointly by the CDC, Department of Health and Human Services (DHHS), the United States Environmental Protection Agency (USEPA), and the American Water Works Association (AWWA). Nor is the term "screening level" used in the Drinking Water Standards and Health Advisories literature (e.g., USEPA, 2012).

According to the CDC document on the 2014 West Virginia Chemical Release (CDC, 2014c), the "screening level" is calculated using the same procedure as a health advisory (HA) level, and, specifically, the drinking water (DW) advisory level. For example, the CDC states (CDC, 2014c) "calculation to establish a short-term *screening level* of 1 part per million (ppm) for the MCHM spill in the Elk River" was: DW *Advisory Level* ≤ (NOEL × BW) / (UF × Intake)" and that the DW Advisory Level is 1 mg/L. In this literature review, we use the terms "screening level" and advisory levels to be consistent with the literature regarding the 2014 West Virginia chemical spill event.

A Health Advisory (HA) is "An estimate of acceptable drinking water levels for a chemical based on health effects information" (USEPA, 2012; Donohue and Lipscomb, 2002). An HA is not legally enforceable from a Federal perspective, but serves as a guideline for state and local officials. A One-Day HA is developed to provide protective (non-carcinogenic) guidance for a child assumed to weigh 10-kg and drinking 1 L/day water over a one-day exposure (USEPA, 2012). A Ten-Day HA is developed to protect a 10-kg child drinking 1 L/day over a ten-day period (USEPA, 2012). A Lifetime HA is the concentration of a chemical that is not expected to cause adverse health effects over a lifetime of exposure for a 70-kg adult drinking 2 L/day (USEPA, 2012).

Two further terms of interest include the Drinking Water Equivalent Level (DWEL), which is defined as (USEPA, 2012) as "...a drinking water lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur." Finally, a reference dose (RfD) is defined as (USEPA, 2012) "...An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime."

1.2 Chemical Products in Spill

Several chemical products were in the spill into the Elk River. Information on these chemicals are summarized briefly in this section, and in more detail below.

1.2.1 Crude MCHM - The Crude MCHM is a mixture containing 4-methyl-1-cyclohexanemethanol (MCHM; CAS 34885-03-5); 4-(methoxymethyl) cyclohexane methanol (MMCHM; CAS 98955-27-2); methyl 4-methylcyclohexane-1-carboxylate (MMCHC; CAS 51181 -40-9); 1,4-dimethyl cyclohexanedicarbonate (DMCHDC; CAS 94-60-0); 1,4-cyclohexanedimethanol (CHDM; CAS 105-08-8); and methanol (MeOH; CAS 67-56-1). According to the Material Safety Data Sheet (MSDS) for Crude MCHM(Eastman MSDS for Crude MCHM, 2005; Eastman MSDS for Crude MCHM, 2011), MCHM (CAS 34885-03-5) is the primary component at 68-89% (w/w), MMCHM (CAS 98955-27-2) is second most concentrated at 4-22% (w/w), MMCHC is at 5% (w/w) and the other constituents are at 1 -2% (w/w) each. Crude MCHM is used in coal processing. Crude MCHM is used for a variety of applications including as a coal and ore flotation chemical (Eastman, 2014a).

1.2.2 DOW PPH Basic—It is reported (thoughnot yet citable) that the source of theFreedom Industries' PPH was DOW PPH Basic(DOW MSDS PPH Basic, 2011) and also described somewhat in the DiPPH Product Data Sheet (DOW DiPPH, 2009). The MSDS for DOW Basic (DOW MSDS PPH Basic, 2009) contains ≤85% DiPPH (CAS 51730-94-0), ≤30% PPH (CAS 770-35-4), ≤ 10% propoxylated impurities, ≤5% 2-hydroxy-alpha-methyl-benzeneethanol (CAS 33206-31-4), ≤5% 2-hydroxy-beta-methyl-benzeneethanol (CAS 134342-25-9), ≤5% polypropylene glycol phenyl ether (CAS28212-40-0), and ≤5% sodium hydroxide (CAS1310-73-2). According to the DiPPH product datasheet (DOW DiPPH, 2009), DOW basic contains >40% dipropylene glycol phenyl ether (DiPPH) (CAS 51730-94-0), which, thus brackets the DiPPH concentration between 40% and 85%, with the remainder being PPH and other compounds. The exact composition of the PPH/DiPPH mixture will likely need to come from Freedom Industries.

Another common source of PPH is the DOWANOL PPH Glycol Ether product from DOW (DOW PPH, 2008; DOW PPH 2013; DOW PPH, 2012; DOW PPH, 2014). The DOWANOL PPH Glycol Ether mixture contains >99.5% pure PPH (CAS 770-35-4) (DOW PPH 2012a). While DOW PPH Basic was the likely source for the PPH (and DiPPH) in the spil l, the citation for DOWANOL PPH Glycol Ether is provided for informational purposes.

Another common source of DiPPH is the DOWANOL DiPPH Gylcol Ether product from DOW (DOW DiPPH, 2009; DOW DiPPH, 2012). The DOWANOL DiPPH Gylcol Ether mixture contains >60% pure DiPPH (CAS 51730-94-0), <25% pure PPH (CAS 770 -35-4), and polypropylene glycol phenyl ether (CAS 28212 -40-0) (DOW DiPPH, 2009). Again, while DOW PPH Basic was the likely source for the DiPPH (and PPH) in the spill, the citation for DOWANOL DiPPH Glycol Ether is provided for informational purposes.

2.0 PURPOSE

The purpose of this literature review is to presenta summary oftoxicity information on the chemicals that were spilled into the Elk River in West Virginia inJanuary 2014 from the Freedom Industries facility. While every effort has been made for accuracy and completeness, the information contained herein should be independently verified, and may contain inaccuracies. The authors and the WV TAP assume no responsibility for use of the information.

3.0 HEALTH DATA ON INDIVIDUAL CONSTITUENTS AND MIXTURES BASED ON EASTMAN TOXICOLOGY STUDIES

3.1 Drinking Water Advisory Based on Crude MCHM and Pure MCHM (CAS 34885-03-5) Studies

The Centers for Disease Control and Prevention (CDC) have suggested a screening level of 1 mg/L (ppm) for MCHM (CAS 34885-03-5), and state (CDC, 2014a):

> "A level of 1 ppm or below is not likely to be associated with any adverse healt h effects." (CDC, 2014a). The CDC release also suggests that pregnant women may consider additional caution.

The CDC calculated this screening level of 1 mg/L (ppm) using traditional drinking water toxicological assumptions for body weights, quantities of water consumed and uncertainty factors (USEPA, 2012; Donohue and Lipscomb, 2002). The CDC apparently intends this "screening" level to be equivalent to an "advisory" level, as they are clearly equated in the following (CDC, 2014c). Specifically, the "calculation to establish a short-term screening level of 1 part per million (ppm) for the MCHM spill in the Elk River(CDC, 2014c) was:

$$\text{DW Advisory Level} \leq (\text{NOEL} \times \text{BW}) / (\text{UF} \times \text{Intake})$$

where:

- DW Advisory Level is the drinking water advisory level (mg/L or ppm)
- NOEL = No Observed Effect Level in the experimental species = 100 mg/kg/day
- BW = body weight of a child = 10 kg
- UF = uncertainty factors (unitless)
  - for differences between humans and animals (10x)
  - to account for more sensitive humans (10x)
  - to account for weaknesses in the toxicological database (10x)
- Intake = estimated quantity of water consumed daily by a 10 kg child (1 L/d)

Thus,

$$\text{DW Advisory Level} \leq (\text{NOEL} \times \text{BW}) / (\text{UF} \times \text{Intake}) = [(100\ \text{mg/kg/d}) \times (10\ \text{kg})] / [(10\times10\times10) \times (1\ \text{L/d})]$$

$$\text{DW Advisory Level} \leq 1\ \text{mg/L (ppm)}$$

The assumptions for BW, UF and Intake are common especially for short-term health advisories (USEPA, 2012).

Very limited toxicological data has been reported for MCHM Crude or pureMCHM (CAS 34885-03-5). The No Observed Effect Level (NOEL) used by the CDC in calculation of their DW Advisory Level was based on studies conducted for the manufacturer, Eastman Chemical in the 1997 and 1998. Eastman released the results of these studies after the Freedom Industries spill in January 2014.

Eastman reports that they perform "regulatory and toxicity review" of all their chemical products (Eastman, 2014a). They report that uses fo r Crude MCHM has been ongoing since the 1970s. Eastman reports that in 1990, "as part of its ongoing review process, Eastman…conducted toxicology studies on pure MCHM (CAS 34885 -03-5)." They state that in 1997, they conducted further toxicological tests of Crude MCHM prior to its release for a co al cleaning application. These studies are listed at Eastman (2014b).

The CDC (CDC, 2014a) relied primarily on two of the Eastman toxicology studies to develop the DW Advisory Level: the 1998 first acute oral study on Crude MCHM (Eastman TX-97-306); and the 28-day oral feeding study on pure MCHM (CAS 34885-03-5) (Eastman TX-89-296).

While the CDC established a recommended screening level of 1 mg/L, the State of West Virginia established "a more stringent testing threshold of 10 parts per billion" (or 10 µg/L) for MCHM (CAS 34885-03-5) (Tomblin, 2014a).

On February 24, 2014, the West Virginia Department of Education issued a press release that stated: "The West Virginia National Guard is revisiting more than 100 schools in Kanawha, Boone, Clay, Cabell, Lincoln and Putnam counties. The results returned so far are indicating a non-detect level at the 2 ppb standard. Non-detect means that there are no traces of MCHM at the 2ppb screening level. After testing thousands of lab samples, chemists are now able to confidently test at 2ppb." (Tomblin, 2014b).

3.1.1 The first acute oral study on Crude MCHM (Feb. 1998; Eastman TX-97-306) was titled "Acute Oral Toxicity Study in the Rat". The tests were performed at Eastman Kodak's Health and Environmental Laboratories in Rochester, NY. The purpose of this study was to estimate the LD_{50} for Crude MCHM in both male and female Sprague-Dawley rats ([SAS:VAF(SD)] obtained from SASCO, Inc.) with a single oral dose .

The rats were dosed with 500 mg/kg, 1,000 mg/kg and 2,000 mg/kg of Crude MCHM and observed for 14 days (Eastman TX-97-306). Each group of male or female rats for each of the three dosing levels consisted of from 50 1 to 540 rats. The results showed that Crude MCHM was a gastric irritant with edema (i.e., accumulation of fluid) in the glandular gastric mucous membrane. Red discoloration of the urine (hematuria) in some test subjects was noted. A combined LD_{50} for males and females was determined to be 825 mg/kg corresponding to a "slightly toxic" designation in the report (Eastman TX-97-306). Individual LD_{50} values were 933 mg/kg and 707 mg/kg for male and female rats, respectively. This two-week study was one of two Eastman studies evaluated by the CDC to develop the DW Ad visory Level (or screening level) of 1 mg/L for MCHM (CAS 34885-03-5) (CDC, 2014a).

A release by Dyer (May 23, 2000) points out some problems, however, with the SAS:VAF(SD) rat s from, SASCO, Inc., used in this study and, states specifically (Dyer, 2000):

> "CRUDE MCHM – Toxicology Assessment (972790): Hematuria was seen in acute oral and dermal toxicity studies of Crude MCHM conducted in August 1997. However, these studies were conducted with the SAS:VAF(SD) rat from S ASCO, Inc. (Stone Ridge (Kingston), NY) , which was used for a short period of time at the Eastman Kodak Company Health and Environment Laboratories. The Laboratories had a number of problems with this strain of rat and returned to using their former animal supplier, Charles River Laboratories. Because of the hematuria finding in the acute studies, a repeated skin application was conducted in CD(SD)BR/VAP Plus rats from Charles River Lab oratories in April 1998 with doses of 2,000 mg/kg/day applied 6 hours/day for 13 c onsecutive days. Full hematology, urinalysis, clinical chemistry, grow pathology, and histopathology examination were included. Other than skin irritation at the site of application, no toxic effects were observed in this detailed examination. An acute ora l study was conducted in female CD(SD)IG BR rates from Charles River Laboratories in November 1999: a single dose of 500 mg/kg did not produce any hematuria. Therefore, the finding in the SASCO rat is considered to be of limited value in risk assessment. [The same sample (97-0216) was used for all studies.]"

3.1.2 The 28-day oral feeding study on pure MCHM (CAS 34885-03-5) report (April 3, 1990; Eastman TX-89-296) was titled: "Four-Week Oral Toxicity Study of 4Methylcyclohexane Methanol in the Rat" Tests were conducted at the Toxicological Sciences Laboratory, Health and Environmental Laboratories,

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Eastman Kodak Co., in Rochester, NY. Regarding statistical procedures, the report states that mean values were calculated for clinical chemistry, hematology, organ weights, feed consumption and body weight. Further, the report states that the mean data (except feed consumption) were evaluated using Barl ett's test (with $p \leq 0.01$, or 99% confidence), one -way analysis of variance (ANOVA) (with $p \leq 0.05$, or 95% confidence), and Duncan's multiple range test (with $p \leq 0.01$, or 99% confidence). Neither the statistical analysis nor control sample data, was presented in the report however.

In the first phase of the study, two male and two female rats were dosed with from 200mg/kg/day to 800 mg/kg/day of pure MCHM (CAS 34885-03-5) in corn oil for five days via gavage (i.e., a tube through nose or mouth to the stomach) . Results of the five -day experiments showed narcosis (i.e., state of stupor or unconsciousness) in one male and two female rats, and ataxia (i.e., lack of muscle control) in the other female rat at the highest dose level (800 mg/kg/day) (Eastman TX-89-296).

This five-day test was followed by a four-week study with dosing of five male and five female rats of from 0 mg/kg/day to 400 mg/kg/day of pure MCHM (CAS 34885 -03-5) five days per week. The report summarizes its results as: "In summary, administration of 400 mg/kg/day of the test article for four weeks was associated with erythropoietic, kidney, and liver effects. None of the effects were indicative of more than minor toxicity, and all were most likely reversible. The no -observed effect level for this substance toxicity study was 100 mg/kg/day." This four-week study was one of two Ea stman studies evaluated by the CDC to develop the DW Advisory Level of 1 mg/L for MCHM (CAS 34885-03-5) (CDC, 2014a).

The CDC stated about the Eastman studies and this 28-day oral feeding test in particular (CDC, 2014b):

> "Together, these studies provide a much -improved (but still incomplete) understanding of MCHM's toxicology profile. In particular, one of the studies, the 4-week rat study (study 5 above), provides a NOEL in rats. This NOEL, established by the authors of the study, is 100 mg/kg/day. The 4-week NOEL represents a more scientifically sound study and point of departure for establishing a short-term health advisory for MCHM."

3.2 Other Pure MCHM (CAS 34885-03-5) Study

The acute toxicity battery (containing 5 study reports) on pure MCHM (CAS 34885-03-5) (Jan. 26, 1990; Eastman TX -90-5) was conducted in 1990 and was titled: "Acute Toxicity of 4 -Methylcyclohexane Methanol." The study was con ducted at the same Eastman Kodak Co. laboratory as the other Eastman 1990 study. The acute toxicity battery study included tests with rats for acute oral toxicity, rats for acute dermal toxicity, guinea pigs for acute toxicity -dermal irritation, guinea pig s for acute toxicity – skin sensitization, and rabbits for acute toxicity-eye irritation. The details of the study may be found with the study report available on-line (Eastman TX-90-5). For the acute oral toxicity in rats testing, LD_{50} values of 1,768 mg/kg and 884 mg/kg were determined for male and female rats, respectively. Remarks from the rat studies included that MCHM (CAS 34885 -03-5) was "slightly toxic by the oral route" and was "moderately toxic by the dermal route." For the guinea pig studies, remarks included that the MCHM (CAS 34885-03-5) was "a strong skin irritant." Remarks for the rabbit study included that MCHM (CAS 34885-03-5) was "a moderate eye irritant."

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3.3 Crude MCHM Studies

The studies conducted by Eastman in 1997, 1998 and 1999 included a wide range of tests, specifically (Eastman, 2014b)

- Acute Minnow Study
- Acute *Daphnia* Study
- Ready Biodegradation Study
- Chemical Oxygen Demand
- Biological Oxygen Demand
- Skin Sensitization
- Ames Assay
- 14-Day Dermal Study
- First Acute Oral Study
- Second Acute Oral Study
- Acute Dermal Toxicity Study
- Skin Irritation Study

3.3.1 The acute minnow study on Crude MCHM (Feb. 10, 1998; Eastman ES-98-004) was titled "An Acute Aquatic Effects Test with the FatheadMinnow-*Pimephales promelas*." The tests were performed at Eastman Kodak's Health and Environmental Laboratories in Rochester, NY. The test was a 96-hr, static, aquatic effects test with exposures ranging from 6.25mg/L to 100 mg/L. The study concluded thatthe 96-hr LD_{50} as 57.4 mg/L and the 96 -hr no-observed-effect concentration (NOEC) was 25 mg/L. The study concluded the 96-hr LD_{50} corresponded to a European Union label as "harmful to aquatic organisms" and to a "moderate concern level" by the USEPA assessment criteria (Eastman, ES-98-004).

3.3.2 The Acute *Daphnia* study on Crude MCHM (Feb. 9, 1998;Eastman ES-98-005) was titled "An acute aquatic effects test with the Daphnid – *Daphnia magna*". The tests were performed at Eastman Kodak's Health and Environmental Laboratories in Rochester, NY. The test was a 48-hr, static, aquatic effects test. The study concluded that the 48-hr EC_{50} for Crude MCHM with *Daphnia magna* was 98.1 mg/L, and the 48-hr NOEC was 50.0 mg/L. The study concluded that 48-hr EC_{50} corresponded to a European Union label as "harmful to aquatic organisms" and to a "moderate concern level" by the USEPA assessment criteria (Eastman, ES-98-004).

3.3.3 The Ready Biodegradation study on Crude MCHM (Dec. 3, 1997; Eastman ES-97-112) was titled "Determination of Ready Biodegradability (Biotic Degradation) u sing the CO_2 evolution test (modified Sturm)." The tests were performed at Eastman Kodak's Health and Environmental Laboratories in Rochester, NY. The 28-day biodegradability test results were that Crude MCHM "could not be classified as readily biodegradable" (Eastman ES-97-112).

3.3.4 The Chemical Oxygen Demand study on Crude MCHM (Oct. 2, 1997; Eastman COD-00775) was titled "Chemical Oxygen Demand Determination". The tests were performed at Eastman Kodak's Health and Environmental Laboratories in Rochester, NY. The results showed a chemical oxygen demand (COD) of 2.54 g COD per g of Crude MCHM (Eastman COD-00775).

3.3.5 The Biological Oxygen Demand Study on Crude MCHM (Sept. 30, 1997;Eastman BOD-00774) was titled "Biochemical Oxygen Demand Determination". The tests were performed at Eastman Kodak's Health and Environmental Laboratories in Rochester, NY. The results showed an average five -day biochemical oxygen demand (BOD_5) of 0.070 g BOD_5 per g Crude MCHM (Eastman BOD-00774). A 20-day

BOD test was also run resulting in a BOD_{20} of 1.3 g BOD_5 per g Crude MCHM (though inhibitory effects were noted except at the most dilute concentrations) (Eastman BOD-00774). The BOD_5/COD ratio was calculated as 0.028 indicating very low biodegradability.

3.3.6 The Skin Sensitization Studyon Crude MCHM (Dec. 12, 1997;Eastman TX-97-271) was titled "Skin Sensitization Study (Footpad Method) in the Guinea Pig ." Tests were performed at Eastman Kodak's Health and Environmental Laboratories in Rochester, NYand did not cause serious lesions over a 48-hour observation period. No sensitization response was found forCrude MCHM. The researchers further noted that no toxic effects or systemic clinical signswere detected. Details of the study are presented inEastman TX-97-271.

3.3.7 The Am es Assay on Crude MCHM (Sept. 12, 1997; Eastman TX -97-241) was titled "In the *Salmonella-Escherichia Coli*/Mammalian-Microsome Reverse Mutation Assay with a ConfirmatoryAssay." Tests were performed at the Covance Laboratories in Vienna, VA. The assay tests for mutagenic activity using *Salmonella Typhimurium* strains and one *E. coli* strains. The conclusions of the test were that the Crude MCHM did not cause a positive incr ease in the number of revertants per plate…either in the presence or absence of microsomal enzymes…", that is, that Crude MCHM was not mutagenic in the assay (Eastman TX-97-241). Eastman claims that 90% of carcinogens are identified by the Ames t est (Eastman, 2014a; CDC, 2014b).

3.3.8 The 14-Day Dermal Study on Crude MCHM (Jan. 6, 1999; Eastman TX-98-129) was titled "A Two-Week Dermal T oxicity Study in the Rat ." Testing was carried -out at Eastman Kodak's Health and Environmental Laboratories in Rochester, NY. The test examined the effect of repeated application of Crude MCHM to the skin of both male and female rats over a two -week period. A NOEL was not determined in the test. However, a no -observed-adverse-effect level (NOAEL) of 2 ,000 mg/kg was determined for systemic toxicity (that is, toxicity associated with absorption of a toxicant) (Eastman TX-98-129).

3.3.9 The Second Acute Oral Study on Crude MCHM (Dec. 1, 1999; Eastman TX -99-188) was titled "Acute Oral Toxicity Study in the Rat ." The tests were performed at Eastman Kodak's Health and Environmental Laboratories in Rochester, NY. The purpose of the test was to determine acute toxicity of Crude MCHM in female Sprague-Dawley rats with a single Crude MCHM oral dose. The test was specifically interested in whether hematuria (i.e., blood in the urine)would be exhibited. Results showed that a single dose of 500 mg/kg did not result ineither death or hematuria (i.e., blood in urine)of the five rats exposed. While the rats appeared clinically normal after both prior to 1 hr and also after 24 hr (for two weeks), at 4 hr reduced activity in all test rats and stumbling in 40% of test rats was noted (Eastman TX-99-188).

3.3.10 The Acute Dermal Toxicity Study on Crude MCHM (Feb. 24, 1998; Eastman TX-97-308) was titled "Acute Dermal Toxicity in the Rat." Testing was conducted at Eastman Kodak's Health and Environmental Laboratories in Rochester, NY. The purpose of the dermal toxicity study was to assess a dermal LD_{50} for Crude MCHM in both male and female Sprague-Dawley rats observed over a two-week period based on a single topical dose of 2,000 mg/kg. The study demonstrated that Crude MCHM was a dermal irritant resulting in focal necrosis (i.e., occurrence of small foci of necrosis) and esch ar (i.e., slough or scab) formation at the application site. An LD_{50} of >2 ,000 mg/kg was determined for Crude MCHM corresponding to "slightly toxic" (Eastman TX-97-308).

(Note: As discussed for the "Acute Oral Toxicity Study in the Rat" study above, arelease by Dyer (May 23, 2000) points out some problems with the SAS:VAF(SD) rat used in this study (Dyer, 2000).)

3.3.11 The Acute Dermal Irritation Study in the Rabbiton Crude MCHM (Nov. 10, 1997; Eastman TX-97-256) was titled "Acute Dermal Irritation Study in the Rabbit ." The tests were performed at Eastman Kodak's Health and Environmental Laboratories in Rochester, NY. The potential for Crude MCHM to irritate mammalian skin was examined during this study using three albino rabbits (Hra: (NZW)SPF) (Eastman TX-97-256) dosed with 0.5 mL of Crude MCHM . Test results revealed that Crude MCHM was "irritating to skin" (Eastman TX-97-256).

3.4 4-(MethoxyMethyl) Cyclohexane Methanol (MMCHM (CAS 98955-27-2))

MMCHM (CAS 98955-27-2) occurs at 4-22% in Crude MCHM . While the toxicity of pure MMCHM (CAS 98955-27-2) was not reported by Eastman, they noted that because MMCHM (CAS 98955-27-2) and MCHM are structurally similar, they would be expected to have similar toxicity (Eastman, 2014a).

4.0 HEALTH DATA ON INDIVIDUAL CONSTITUENTS AND MIXTURES FROM TOXNET SOURCES

4.1 MCHM (CAS 34885-03-5)

TOXNET relied on the Eastman toxicology studies cited above for toxicity and health effects information for MCHM (CAS 34885-03-5) (TOXNET – MCHM, 02/25/14).

4.2 4-(MethoxyMethyl) Cyclohexane Methanol (MMCHM (CAS 98955-27-2))

No pure MMCHM (CAS 98955-27-2) toxicity data were found.

4.3 Methyl 4-MethylCyclohexane-1-carboxylate (MMCHC (CAS 51181-40-9))

No pure MMCHC (CAS 51181-40-9) toxicity data were found.

4.4 1,4-Dimethyl CycloHexaneDicarbonate (DMCHDC (CAS 94-60-0))

DMCHDC (CAS 94-60-0) is a Crude MCHM constituent (Eastman, 2011). The MSDS for DMCHDC (CAS 94-60-0) (Sigma 2013) states that there is no data available for oral LD_{50}, inhalation LD_{50}, dermal LD_{50}, skin corrosion/irritation, serious eye damage/eye irritation, respiratory or skin sensitisation, germ cell mutation, reproductive toxicity, teratogenicity, nor other measures.

For DMCHDC (CAS 94-60-0), TOXNET states that "a specific review of the clinical effects and treatment of individuals exposed to this agent HAS NOT YET BEEN PREPARED." TOXNET goes on to state general evaluation information regarding irritation, hypersensitivity and other effects (TOXNET-dimethyl hexahydroterephalate (CAS 94-60-0).

4.5 1,4-CycloHexaneDimethanol (CHDM (CAS 105-08-8))

Similarly, CHDM (CAS 105-08-8) is a Crude MCHM constituent (Eastman, 2011). The MSDS for CHDM (CAS CAS 105-08-8) (Sigma 2012) states an oral LD_{50} for rats of 3,200 mg/kg. The MSDS also states that there is no data available for inhalation LD_{50}, dermal LD_{50}, skin corrosion/irritation, serious eye damage/eye irritation, respiratory or skin sensitisation, germ cell mutation, reproductive toxicity, ter atogenicity, nor other measures.

For CHDM (CAS 105-08-8), TOXNET states that "a specific review of the clinical effects and treatment of individuals exposed to this agent HAS NOT YET BEEN PREPARED." TOXNET goes on to state general

evaluation information re garding irritation, hypersensitivity and other effects (TOXNET-1,4-cyclohexanedimethanol (CAS 105-08-8)).

5.0 TOXICOLOGY DATA AVAILABLE ON EPA ACToR

The USEPA has de veloped a system called Aggregated Computational Toxicology Resource (ACToR) to house publicly available toxicity information. The database includes data from ToxRefDB, ToxCastDB, ExpoCastDB, and DSSTox (USEPA, 2014).

5.1 4-Methyl-1-CyclohexaneMethanol (MCHM; CAS 34885-03-5)

No toxicology data were listed (http://actor.epa.gov/actor/GenericChemical?casrn=34885-03-5).

5.2 4-(MethoxyMethyl) Cyclohexane Methanol (MMCHM; CAS 98955-27-2)

No toxicology data was listed (http://actor.epa.gov/actor/GenericChemical?casrn=98955-27-2).

5.3 Methyl 4-MethylCyclohexane-1-Carboxylate (MMCHC; CAS 51181-40-9)

No toxicology data was listed (http://actor.epa.gov/actor/GenericChemical?casrn=51181-40-9).

5.4 1,4-Dimethyl CyclohexaneDicarbonate (DMCHDC; CAS 94-60-0)

The EPA ACToR database documented a large number of studies for this minor constituent (1%) of Crude MCHM. The studies were conductedat various laboratories including Eastman. The studies generally note low or slight toxicity for CHDM (CAS 105 -08-8) (check this). The reader is referred to the EPA ACToR document for details of the many studies (http://actor.epa.gov/actor/GenericChemicalPdfServlet?casrn=94-60-0).

5.5 1,4-CycloHexaneDimethanol (CHDM; CAS 105-08-8)

The EPA ACToR database documented a large number of studies for this minor constituent (2%) of Crude MCHM. The studies were conductedat various laboratories including Eastman. The studies generally note low or slight toxicity for DMCHDC (CAS 94 -60-0) (check this). The reader is referred to the EPA ACToR document for details of the many studies (http://actor.epa.gov/actor/GenericChemicalPdfServlet?casrn=105-08-8).

5.6 Methanol (MeOH; CAS 67-56-1)

A large amount of toxicology data is available for methanol (http://actor.epa.gov/actor/GenericChemical?casrn=67-56-1).

5.7 PPH (770-35-4)

No toxicology data were listed for PPH.

5.8 DiPPH (CAS 51730-94-0)

No toxicology data were listed for DiPPH.

5.9 Polypropylene glycol phenyl ether (CAS 28212-40-0)

No toxicology data were listed for polypropylene glycol phenyl ether.

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6.0 FREEDOM INDUSTRIES "PPH STRIPPED"

6.1 Release of Information

Days following the Crude MCHM tank chemical spill, Freedom Industries disclosed that in addition to Crude MCHM, a second liquid product was also present in the tank that leaked called "PPH Stripped" (Freedom Industries, October 15, 2013). The MSDS for PPH Stripped listed its composition as "polyglycol ethers" at 100% with the CAS number shown as "proprietary" (and "being withheld as a "trade secret" in accordance with 29 CFR 1910.1200(i)."). It was later disclosed that the polyglycol ethers were a mixture of polypropylene glycol phenyl ether (PPH (CAS 770-35-4)) and dipropylene glycol phenyl ether (at 7.3% by weight in the total mixture in the tank) (CDC 2014a). The PPH (CAS 770-35-4) in PPH Stripped may have been originally purchased as DOWANOL PPH Glycol Ether (DOW PPH (2008)) and processed before being combined with Crude MCHM . The MSDS for DOWANOL PPH Glycol Ether (DOW PPH, 2013) states the product contains >99.5% PPH (CAS 770-35-4).

DOW states that they sellDiPPH (CAS 51730-94-0) in "several commercial products...including DOW DPPH Technical and DOW PPH Basic" containing 75% and 40%, respectively, Di PPH (DOW DiPPH, 2009). DOW states that other constituents include PPH (CAS 770 -35-4) and "other reaction products" (DOW DiPPH, 2009). Thus, it is not fully clear what, if any, other ethers (in addition to PPH (CAS 770 -35-4) and DiPPH (CAS 51730-94-0)) were present in the liquid mixture that leaked into the Elk River, which is dependent on the source or products containing PPH (CAS 770-35-4) and DiPPH (CAS 51730-94-0) that were used by Freedom Industries. For example, if the DiPPH (CAS 51730-94-0) in the Freedom Industries tank (and spill) were purchased as DOW dipropylene glycol phenyl, it appears to also contain a third ether, polypropylene glycol phenyl ether (CAS 28212-40-0) ether (DOW DiPPH, 2012).

The CDC notes that limited toxicological data are available forPPH (CAS 770-35-4) and DiPPH (CAS 51730-94-0). The MSDS for both compounds are prepared by the manufacturer (D OW Chemical) and provided some relevant information. For example, the acute oral LD_{50} (rat) is reported by Freedom Industries (October 2013) to be >2,000 mg/kg (for the PPH (CAS 770-35-4)) (CDC, 2014a). Similarly, the dermal LD_{50} (rat) is reported to be greater than 2 ,000 mg/kg (for the Stripped PPH) (Freedom Industries, 2013). The document also states that PPH (CAS 770-35-4) is not reported to be a carcinogen. The source of studies for the reported Freedom Industries data is not provided.

The data appear to show that both PPH (CAS 770-35-4) and DiPPH (CAS 51730-94-0) are less toxic than Crude MCHM (CDC, 2014a). Specifically, the acute oral LD_{50} (rat) for PPH (CAS 770-35-4) is greater than 2,000 mg/kg (Freedom Industries, 2013) versus 825 mg/kg for Crude MCHM (Feb. 1998; Eastman TX-97-306).

6.2 PPH (CAS 770-35-4)

The MSDS PPH (DOW PPH, 2013) states that the toxicity is low if ingested and that animal toxicity studies "were predominantly negative" . The MSDS states that PPH (CAS 770 -35-4) has caused birth defects in laboratory animals only at levels that were toxic to the mother (DOW PPH, 2013). The LD_{50} for PPH (CAS 770-35-4) is reported at 2,000 mg/kg. It is also stated thatPPH (CAS 770-35-4) can cause severe eye injury and irritation, and skin irritation. The MSDS states no chronic toxicity or carcinogenicity data were found. The MSDS states that birth defects only occurred at doses toxic to the mother, and thatPPH (CAS 770-35-4) did not interfere with reproduction in reproductive animal studies. The MSDS for PPH (CAS 770-35-4) reported an LC_{50} for fathead minnows of 280 mg/L in a 96 -hour static test. For *Daphnia magna* (water

flea), a LC_{50} of 370 mg/L for a 96-hr static test was determined. Biodegradation tests for PPH (CAS 770-35-4) showed 28% biodegradation in 28 days.

6.2.1 CDC Drinking Water Advisory for PPH - The CDC calculated its PPH drinking water screening level of 1.2 mg/L (ppm) (CAS 770-35-4) in a manner similar (but slightly different) to that reported for MCHM above. Specifically, the drinking water advisory level (DW Advisory Level) was calculated as (CDC, 2014d):

DW Advisory Level ≤ (NOAEL × BW) / (UF × Intake)

where:

- DW Advisory Level is the drinking water advisory level (mg/L or ppm)
- NOAEL = No Observed Effect Level in the experimental species = 40 mg/kg/day
- BW = body weight of a pregnant mother = 75 kg
- UF = uncertainty factors (unitless)
    - for differences between humans and animals (10x)
    - to account for more sensitive humans (10x)
    - to account for in the toxicity database data (10x)
- Intake = estimated quantity of water consumed daily by a 75 kg pregnant mother (2.5 L/d)

Thus,

DW Advisory Level ≤ (NOEL × BW) / (UF × Intake) = [(40 mg/kg/d) × (75 kg)] / [(10×10×10) × (2.5 L/d)]

DW Advisory Level ≤ 1.2 mg/L (ppm)

The assumptions for BW, UF and Intake are reasonable and common assumptions of the especially for short-term health advisories USEPA (USEPA, 2012).

6.2.2 OECD SIDS data for PPH (CAS 770 -35-4) - The Organization for Economic Cooperation and Development/Screening Information Data Set (OECD SIDS) report titled "Propylene Glycol Phenyl Ether" provides the results of many detailed toxicological studies on PPH (CAS 770 -35-4) as well as two related compounds (CAS 4169-04-4; CAS 41593-38-8) including (but not limited to) (OECD/SIDS, 2006):

- Acute Oral Toxicity in rats,
- Acute inhalation toxicity in rats,
- Acute dermal toxicity in rabbits,
- Eye irritation in rabbits,
- Sensitization in guinea pigs,
- Repeated dose toxicity in rabbits,
- Genetic toxicity "In Vitro" in *Salmonella typhimurium*,
- Genetic toxicity "In Vivo" in mice,
- Toxicity to fertility in rats, and
- Developmental toxicity and teratogenicity in rabbits.

No relevant human exposure information was included. A brief summary of these studies a ccording to this Organization for Economic Cooperation and Development/Screening Information Data Set (report (OECD/SIDS, 2006), is that PPH (CAS 770-35-4) is absorbed, metabolized and eliminated via urine and feces rapidly after oral exposure (OECD/SIDS, 2006; Saghir et al., 2003). PPH (CAS 770-35-4) has low oral and inhalation toxicities with a 2 ,000 mg/kg oral LD_{50} in rats, and a 5 ,400 mg/m^3 4-hr inhalation LD_{50} in rats (OECD/SIDS, 2006). The document noted that PPH (CAS 770 -35-4) was a severe eye irritant, but not a

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dermal irritant in rabbits. In the OECD document, a study was cited that concludes PPH (CAS 770-35-4) only caused effects at the highest exposure concentration of 478 mg/kg/d (OECD/SIDS, 2006).

The NOAEL for drinking water based on a rat study (OECD/SIDS, 2006) was set to 1 ,000 mg/L (or 1 13 mg/kg/d) while the LOAEL was set to 5 ,000 mg/L (or 478 mg/kg/d) based on changes in body weight (OECD/SIDS, 2006). In another study, dermal exposure in rabbits was used to establish a NOAEL of 1,000 mg/kg/d.

In a two -generation study, no adverse effects were found with respect to fertility, reproductive performance, or reproductive tissue (OECD/SIDS, 2006). Specifically, a NOAEL and a LOAEL for maternal toxicity of 180 mg/kg/d and 540 mg/kg/d were established, respectively (OECD/SIDS, 2006).

It was further determined that PPH (CAS 770-35-4) was negative with respect to the Ames *Salmonella* assay (for mutagenicity) (OECD/SIDS, 2006; Bootman and May, 1985; BASF AG, 1996) and negative in an *in vitro* chromosome aberration study with lymphocytes (OECD/SIDS, 2006; Bootman, 1986).

Details of these studies may be found in OECD SIDS (2006) report.

6.2.3 Other Toxicity Data for PPH - A paper by Greenman (1984), infers that the sub -lethal concentration for the stud y bacterium was 0.1 % w/v, where as 0.2% caused complete inhibition of the bacterium. The BIBRA working group (1992) states that PPH (CAS 770-35-4) was "of low acute oral toxicity in rats, and was only a minimal irritant for dermal exposure in rats, but was an irritant for the eyes of rabbits (cited in TOXNET as BIBRA working group, 1992).

A SIDS Initial Assessment Report for SIAM 18 (2004) reports toxicology data for a mixture of PPH isomers (CAS 770-35-4 (major isomer), CAS 4169 -04-4 (minor isomer), and CAS 41593 -38-8 (commercial mixed isomer product) (BIBRA, 2014).

6.2.4 DiPPH (CAS 51730 -94-0) - The MSDS for DOWANOL DiPPH Glycol Ether is for a mixture of approximately 60% DiPPH, 25% PPH (CAS 770 -35-4), and 15% polypropylene glycol phenyl ether. The MSDS states that neither ingestion nor dermal LD_{50} values for the mixture have been determined, but for pure DiPPH (CAS 51730-94-0) the values were both >2000 mg/kg (the same reported values as for PPH (CAS 770-35-4)). Similar to PPH (CAS 770-35-4), DiPPH (CAS 51730-94-0) is an eye and skin irritant. The MSDS states that no chronic toxicity nor carcinogenicity data are available. Developmental, reproductive and genetic toxicity were reported identically to PPH (CAS 770-35-4).

The MSDS reported pure DiPPH (CAS 51730-94-0) was "practically non-toxic" to aquatic organisms on an acute basis. The LC_{50} for rainbow trout was 204 mg/L in a 96-hr static test. The aquatic invertebrate acute toxicity had the EC_{50} for *Daphnia magna* of 336 mg/L in a 48-hr static test.

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