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WV TAP
WEST VIRGINIA TESTING ASSESSMENT PROJECT

Report of Expert Panel Review of Screening Levels for Exposure to Chemicals from the January 2014 Elk River Spill

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NOTE

This report was drafted by scientists of Toxicology Excellence for Risk Assessment (TERA) and then reviewed and finalized by the panel members. The members of the panel served as individuals, representing their own personal scientific opinions. They did not represent their companies, agencies, funding organizations, or other entities with which they are associated. Their opinions should not be construed to represent the opinions of their employers or those with whom they are affiliated.

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EXECUTIVE SUMMARY

An independent expert panel met on March 31, 2014 in Charleston West Virginia to review and discuss available toxicity data on chemicals released to the Elk River in January 2014 from the Freedom Industries storage tank. The expert panel and meeting were organized by Toxicology Excellence for Risk Assessment (TERA) under contract to Corona Environmental Consulting for the West Virginia Testing Assessment Project (WV TAP). The panel discussed the initial screening value of 1 ppm (or 1,000 ppb) for 4-methyl-1-cyclohexanemethanol (MCHM), which was developed by the United States (US) Centers for Disease Control and Prevention (CDC) for the State of West Virginia. The panel evaluated the currently available data and developed short-term health advisories for MCHM, propylene glycol phenyl ether (PPH) and dipropylene glycol phenyl ether (DiPPH). They also identified data gaps and made recommendations for additional studies and analyses to reduce uncertainty.

The WV TAP mission is to provide an independent scientific assessment of the spill of crude MCHM into the Elk River and its distribution throughout the nine counties served by West Virginia American Water (WVAW). The project consists of four tasks: (1) an in-depth analysis to determine the odor threshold for MCHM; (2) an initial assessment of the concentration and variability of MCHM at the taps in homes, to be used to design a statistically robust sampling plan for the entire affected area; (3) establishment of an independent panel of experts to evaluate the screening level for MCHM (this expert panel); and, (4) an assessment of the breakdown products that may have been created as a result of the oxidation of crude MCHM by chlorine and potassium permanganate. Members of the WV TAP team provided the expert panel with a brief description of their findings to provide context for the panel.

In preparation for the meeting, the expert panel reviewed the available toxicological data in order to discuss the following charge questions:

- Given data now available, what would be appropriate screening levels for MCHM and PPH in drinking water?
- What additional data, analyses, or studies might reduce uncertainty and provide greater confidence?
- How should the presence of multiple chemicals in the release to the Elk River be considered?
- Are the screening values protective for all potential routes of exposures (i.e., ingestion, dermal and inhalation)?
- Please identify any additional scientific issues or questions that the panel should discuss.

The panel recognized that the CDC used the United States Environmental Protection Agency (US EPA) Health Advisory method (as described in Donohue and Lipscomb 2002) to develop their screening levels for MCHM and PPH. They recognized that the method CDC employed was a traditional approach that used reasonable and common assumptions to develop health protective drinking water health advisory levels. The panel drew upon its collective experience, however, to discuss and consider other organizations' methods and approaches that might be suitable for developing health advisories for the Elk River spill.

People in the affected area have been exposed to MCHM through their community water supply and use this water for multiple purposes. People were exposed to the contaminated water through direct ingestion, but also on the skin, and through inhalation. The panel thought that these other routes of exposure should be considered in setting short-term health advisories, to the extent possible.

The panel reviewed the available data on crude and pure MCHM and recognized that there were limited toxicology data for MCHM. They agreed with the judgment of CDC that the 4-week oral study in rats with pure MCHM (Eastman, 1990), and the 100 mg/kg-day no observed effect level (NOEL), was the most appropriate available study and end point to establish a short-term health advisory for MCHM. However, the expert panel chose to adjust this 100 mg/kg-day experimental dose to account for the dosing regimen of five days per week. In addition, the expert panel determined that without information on what life stage is most sensitive to the effects of MCHM, the health advisory should be designed to protect the most exposed life stage that consumes the most water on a body weight basis, that is, a formula-fed infant of 1- 3 months.

For MCHM, the panel recommended a short-term health advisory of 120 ppb (120 µg/L). This value was recommended for public health use with the 2014 Elk River spill and the subsequent contamination of the local water supply. The advisory is based on the following calculations:

- Use the NOEL of 100 mg/kg-day from the 4 week study of MCHM dated April 3, 1990 by Eastman Kodak (Eastman, 1990).
- Adjust this NOEL to 72 mg/kg-day by multiplying by a factor of 21 days/29 days (0.72) to account for the fact that the rats were only dosed for 5 days per week.
- Divide this adjusted NOEL by a 1000-fold uncertainty factor to estimate a short-term reference dose of 0.07 mg/kg-day (rounded from 0.072); this factor consists of factors of 10 for interspecies adjustment, intraspecies adjustment, and database deficiencies (i.e., missing developmental and reproductive toxicology studies and a second species repeat dose study monitoring systemic toxicity).
- Divide this short-term reference dose by consumption of 0.285 liters of water per kg of body weight per day (US EPA 2011b), representing the 95th percentile of water intake for formula-fed infants (the most exposed population); and then multiply this by 0.5 (Relative Source Contribution, RSC) to allow for other possible sources and routes of exposure, such as dermal and inhalation.
- The resulting short-term health advisory is 120 ppb (rounded to two significant digits).

The panel determined that the development of a lifetime Reference Dose (RfD) or similar chronic duration toxicity value for MCHM would be difficult at the present time, because the longest duration toxicology study is only 4 weeks.

CDC developed a short-term screening level of 1200 ppb for PPH and indicated that this level would also be protective for DiPPH. The panel reviewed the available information on PPH and DiPPH. They considered the prenatal developmental toxicity study using gavage administration that was used by the CDC, but also considered two other studies: a 90-day drinking water study in rats and a two-generation

drinking water study in rats. The panel thought that the no effect levels from each of these three studies should be considered as potential points of departure to derive a short-term health advisory. The panel selected the no observed adverse effect level (NOAEL) of 146 mg/kg-day from the 90-day drinking water study (ECHA, 2014a) to be the best estimate of the boundary between effect and no effect when assessing the available studies as a group. Even though this NOAEL of 146 mg/kg-day is greater than the NOAEL of 40 mg/kg-day identified in the developmental toxicology study used by CDC, the panel thought it was the better choice for the point of departure because the combination of experimental no effect level with the appropriate water intake for infants resulted in a lower value upon which to apply the uncertainty factors. As with MCHM, the toxicological data did not provide evidence that a particular life stage was more or less sensitive or susceptible to adverse effects from exposure to PPH than other life stages, and so the panel used the life stage with the greatest water consumption on a per kilogram body weight basis, that is the formula-fed infant.

The panel recommended a short-term health advisory of 880 ppb (880 µg/L) for PPH. This value was recommended for public health protection use with the 2014 Elk River spill and the subsequent contamination of the local water supply.

- Use the NOAEL of 146 mg/kg-day from the 90-day drinking water study (ECHA, 2014a).
- Divide this NOAEL by a 300-fold uncertainty factor to estimate a short-term reference dose of 0.5 mg/kg-day (rounded from 0.487). This factor consisted of multiples of 10 for interspecies adjustment and intraspecies adjustment, and a factor of 3 to account for data deficiencies (i.e., incomplete database, e.g., missing a second repeat dose toxicology study).
- Divide this short-term reference dose of 0.5 mg/kg-day by consumption of 0.285 liters of water per kg of body weight per day, which represented the 95th percentile of water intake for formula-fed infants (the most exposed population); and then multiply this by 0.5 (RSC) to allow for other possible sources and routes of exposure, such as dermal and inhalation. The resulting short-term health advisory for PPH is 880 ppb (rounded to two significant digits).

The expert panel discussed the available information on DiPPH and agreed that there is some evidence that DiPPH is structurally similar to PPH and that it would be appropriate to use the PPH results to estimate a DiPPH value. The panel agreed that a DiPPH short-term health advisory could be estimated from the PPH data, but that the uncertainty factor for database (UF_D) should be a full factor of 10, rather than 3, to reflect the greater uncertainty in the DiPPH database.

The panel recommended a short-term health advisory of 260 ppb (260 µ/L) for DiPPH. This value is recommended for public health protection use with the 2014 Elk River spill and the subsequent contamination of the local water supply.

- Use the NOAEL of 146 mg/kg-day from the 90 day drinking water study of PPH (ECHA, 2014a);
- Divide this NOAEL by a 1000-fold uncertainty factor. This factor consists of multiples of 10 for interspecies adjustment, intraspecies adjustment, and to account for data deficiencies (e.g.,

missing many studies); then divide by consumption of 0.285 liters of water per kg of body weight per day, which represented the 95th percentile of water intake for formula-fed infants (the most exposed population); then multiply this by 0.5 (RSC) to allow for other possible sources and routes of exposure, such as dermal and inhalation.

- The resulting short-term health advisory for DiPPH is 260 ppb (rounded to two significant digits).

The panel was asked to discuss how the presence of multiple chemicals in the release to the Elk River (i.e., crude MCHM, PPH and DiPPH) should be considered in the derivation or application of the screening values. They noted that in a situation such as this, where toxicity data were not available for the mixture of concern (i.e., the tank contents), nor for a similar mixture, combining the toxicity of the individual components would be a reasonable approach to evaluate the mixture toxicity. The panel thought that for these chemicals, the toxicity of their mixture could be approached by simple additivity of each component. In the case of crude MCHM, the panel thought that it was reasonable to assume its toxicity would be similar to the toxicity of pure MCHM.

Charge Question 4 addressed people using contaminated water for multiple purposes and through multiple routes of exposure. The panel recognized that people are exposed to the contaminated water in various ways, and attempted to account for these additional exposures by including an extra factor (i.e., relative source contribution or water allocation factor) in the calculation of the short-term health advisories discussed in this report.

The panel discussed what additional data, analysis, or research might help reduce uncertainty. They identified two research or data needs specifically for MCHM and suggested three other areas where further analysis and research would aid in better understanding the hazard and risk from this spill.

1. Undertake research to determine what level of MCHM in water would cause skin irritation in humans. The panel recognized that the experimental animal results might be consistent with the patient surveillance reports, but that the available data were not sufficient to estimate a threshold for dermal irritation. The panel recommended that further research be undertaken to determine the potential concentrations of MCHM in water that could cause skin irritation in humans.

2. Conduct toxicology studies for MCHM in pregnant animals. The panel was concerned about the lack of any animal data on developmental toxicity hazard and they recommended that a developmental study in rodents would be useful to evaluate the potential for MCHM to act as a specific developmental toxicant.

3. Organize all available data on exposures and health effects (from immediately following the spill) to facilitate the estimation of initial conditions. The panel understood that multiple parties measured concentrations of the chemicals in the river, water plant and finished water. The panel recommended that data be collated and analyzed to better understand and estimate exposure. In addition, data related to symptom reports should also be analyzed together with the monitoring data to better understand exposure and effects.

4. Pending results of #2 and #3, consider the need for long-term health effects study. If the studies in recommendation #2 show developmental effects that are specific to MCHM and not due to maternal toxicity, and a reliable estimate of exposure can be developed (#3) then the panel would recommend consideration of conducting a longer-term health effects (epidemiology) study.

5. Determine chemical fate and transport within the treatment plant and water distribution system. The panel recommended additional research be conducted on chemical fate and transport of the chemicals, to better understand how the chemicals in the spill interact with other chemicals in the water and the water distribution system.

The panel reviewed available data for MCHM, PPH, and DiPPH and developed short-term health advisories for public health use with the 2014 Elk River spill and the subsequent contamination of the local water supply. Each of the screening values was intended to protect all portions of the population, including infants, children, and pregnant women. Each value is meant to protect for exposures to the water through direct ingestion, inhalation from showering and household water use, skin exposure, and incidental exposures such as brushing teeth. The MCHM advisory is based upon a 28-day rodent study and with the appropriate uncertainty factors is appropriate to use for human exposure situations of one day up to approximately 3 months. The PPH and DiPPH advisories are based upon a 90-day rodent study and a formula-fed infant scenario, and therefore they are also appropriate to use in situations from one day up 3 months. Panel members thought that these values may also be useful for longer exposures, but this would entail determination of the most appropriate water intake to match the exposure duration of interest.

The panel reviewed the CDC screening values and concluded that the CDC used traditional methods and reasonable assumptions of the US EPA Health Advisory program to develop their screening levels. This expert panel's conclusions are not incompatible with the CDC values; the panel used more refined methods to calculate the short-term advisories, including an adjustment to account for additional routes of exposure (dermal and inhalation). The panel developed these short-term health advisories for public health use with the 2014 Elk River spill and the subsequent contamination of the local water supply.

The panel's advisories each have two digits of precision. While guidance is often provided to express these advisories at the level of one significant digit, the panel chose to include two digits to aid in the reader following the calculations and understanding the results.

This meeting report is a summary, not a transcript of the discussions. This final report reflects the panel's final opinion and conclusions. The final recommendations for toxicity values differ slightly from the preliminary report due to rounding to an appropriate level of precision during the calculations.

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Report of Expert Panel Review of Screening Levels for Exposure to Chemicals from the January 2014 Elk River Spill

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INTRODUCTION

This meeting of an independent expert peer review panel has been organized by Toxicology Excellence for Risk Assessment (TERA*)*. TERA is an independent non-profit organization whose mission is to support the protection of public health by developing, reviewing, and communicating risk assessment values and analyses, improving risk methods through research, and educating risk assessors and managers and the public on risk assessment issues. TERA has organized and conducted peer reviews for private and government sponsors since 1996 (see http://www.tera.org/Peer/index.html for information about TERA's program). TERA organized and conducted this expert review under contract to Corona Environmental Consulting for the West Virginia Testing Assessment Project (WV TAP).

TERA independently selected and convened a panel of five experts to review and discuss the available toxicology data and the scientific support for the West Virginia (WV) Screening Level established at 10 parts per billion (ppb). The panel discussed the initial starting value of 1 part per million (ppm), or 1,000 ppb, established by the United States (US) Centers for Disease Control and Prevention (CDC) and the currently available data. They identified data gaps and made recommendations for additional studies or analyses that could strengthen the screening level and reduce uncertainty. The expert panel sought to reach consensus or common agreement on the scientific issues and conclusions.

The panel drew upon the scientific review document authored by Utah State University Professor Craig Adams. The document can be found on the WV TAP website (http://www.dhsem.wv.gov/wvtap/Pages/default.aspx) and is entitled *Health Effects for Chemicals in 2014 West Virginia Chemical Release: Crude MCHM Compounds, PPH and DiPPH. Version 1.5.* The document provides a literature review summarizing toxicity information on the chemicals involved in the spill into the Elk River in January 2014 from the Freedom Industries facility. The chemicals included 4-methyl-1-cyclohexanemethanol (MCHM) (CAS 34885-03-5), propylene glycol phenyl ether (PPH) (CAS 770-35-4), and dipropylene glycol phenyl ether (CAS 51730-94-0) (DiPPH). Crude MCHM is the mixture of MCHM and other compounds.

The independent expert panel included five scientists with expertise in the key disciplines and areas of concern for toxicology evaluation. Each panelist is a well-respected scientist in his field. The panel members have training and experience in the various scientific disciplines involved in evaluating the safety of chemicals in water. Collectively, the panel members are experts in toxicology, derivation of health advisories, human health risk assessment, and water contaminants and systems. They have experience in academia, government, research, and non-profit sectors, which provided a diversity of perspectives for the discussions. TERA questioned each candidate on his current and past relationships with potentially interested parties to identify any potential conflicts of interest. TERA was solely responsible for the selection of the panel members. The experts served as individual scientists and represented their own personal scientific opinions. They did not represent their companies, agencies, funding organizations, or other entities with which they are associated. Short biographical sketches and conflict of interest statements for panel members are provided in Appendix A.

In preparation for the meeting, the expert panel reviewed the Adams et al. literature review and other pertinent information. TERA provided the panel with a list of key questions (the "charge to peer reviewers") to help focus the discussions. The charge questions are briefly described below. A copy of the full charge is found in Appendix B, along with other meeting materials:

- Given data now available, what would be appropriate screening levels for MCHM and PPH in drinking water?
- What additional data, analyses, or studies might reduce uncertainty and provide greater confidence?
- How should the presence of multiple chemicals in the release to the Elk River be considered?
- Are the screening values protective for all potential routes of exposures (i.e., ingestion, dermal and inhalation)?
- Please identify any additional scientific issues or questions that the panel should discuss.

The meeting opened with a welcome by Ms. Jacqueline Patterson of TERA. She described the background and purpose of the expert review and the agenda for the meeting. The panel members then introduced themselves and noted whether they had additions or changes in their conflict of interest statements. None of the panel members had any questions regarding one another's' conflict of interest statements or substantive changes to their own statements.

Dr. Dourson, the panel chair, then described how the meeting would be conducted. He explained that discussions would be organized around the charge questions and would follow the order in the agenda (see Appendix B). He noted that panelists were expected to share their scientific opinions on the discussion questions and panel members were encouraged to question one another to make sure that they understand the scientific basis for one another's opinions. The panel was asked to seek agreement, but if agreement was not possible, the meeting report would note this. He explained that the WV TAP representatives would make a brief presentation on the WV TAP project and results, and answer clarifying questions from the panel. The WV TAP representatives would also be permitted to ask clarifying questions of the panelists to ensure clarity and understanding of the panel conclusions.

TERA drafted this meeting report to provide a summary of the expert panel's discussions and conclusions, and to serve as the official record of the expert review. The draft report was reviewed and revised by the panel members and the final report was approved by the panel. The meeting report is a summary, not a transcript of the discussions. Opinions and comments of panel members are summarized to describe the scope and breadth of the discussions. Individual panelist comments are not identified by name, as it is the conclusions of the panel as a whole that is the value of a peer review meeting. When the panel did not reach consensus on a recommendation, this has been noted. Preliminary conclusions from the panel's discussions were reported on April 1, 2014 in a public meeting in Charleston, West Virginia (see Appendix C for slides used in that presentation). This final report reflects the panel's final opinion and conclusions. The final recommendations for toxicity values differ slightly from the preliminary report due to rounding to an appropriate level of precision during the calculations.

PRESENTATION

Mr. Jeffrey Rosen, Dr. Andrew Whelton, and Dr. Michael McGuire of the WV TAP team began the meeting with a short overview presentation to explain the WV TAP project and present a summary of their findings. Slides from their presentations are found in Appendix D. The WV TAP project mission is to provide an independent scientific assessment of the spill of MCHM into the Elk River and its distribution throughout the nine counties served by West Virginia American Water (WVAW). The project consisted of four tasks: (1) an in-depth analysis to determine the odor threshold for MCHM; (2) an initial assessment of the concentration and variability of MCHM at the taps in homes, to be used to design a statistically robust sampling plan for the entire affected area; (3) establishment of an independent panel of experts to evaluate the safety factor for MCHM; and, (4) an assessment of the breakdown products that may have been created as a result of the oxidation of crude MCHM by chlorine and potassium permanganate. Figure 1 below shows how the four parts of the project fit together. The team members presented results from the first two tasks and preliminary results of the fourth task.

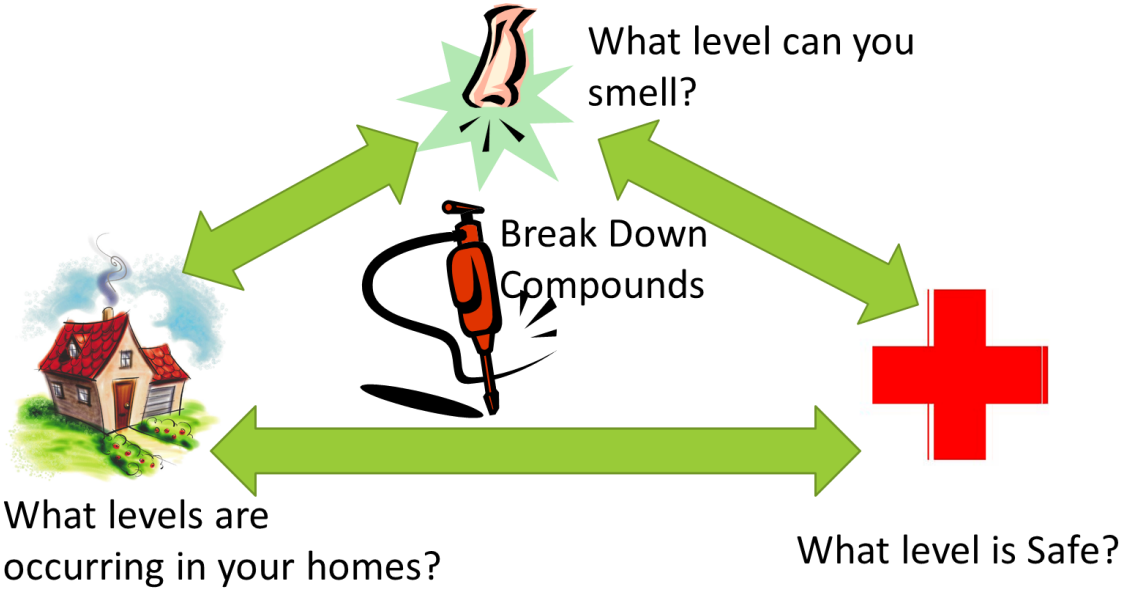

Figure 1. WV TAP Program Mission

Research on an odor threshold for MCHM was designed and conducted by Dr. Michael McGuire of Michael J. McGuire, Inc, along with Dr. I. H. (Mel) Suffet of the University of California, Los Angeles. The objectives of this task were to develop a method to estimate odor thresholds and convene a panel of odor experts to estimate threshold concentrations of detection, recognition, and objection (complaint). The results will be used to understand and explain consumer observations. Dr. McGuire's team used samples of crude MCHM that came from the tank that was the source of the spill. They used ASTM

E679-04 method (ASTM 2011) and trained experts to determine the three thresholds (calculated using geometric mean):

- Odor Threshold Concentration (OTC) - less than 0.15 ppb
- Odor Recognition Concentration (ORC) - 2.2 ppb
- Odor Objection Concentration (OOC) (Based on Degree of Liking) - 4.0 ppb and Odor Objection Concentration (OOC) (based on Objection/Complaint) - 4.0 ppb

The estimated thresholds support consumer observations in Charleston, WV that people could recognize and objected to the licorice odor caused by crude MCHM in their drinking water even though the analytical reports were showing non-detect at a minimum reporting level of 10 ppb.

The second task was to conduct a focused residential drinking water sampling field study to be used to support the design of a larger more comprehensive program for the nine counties affected. Dr. Andrew Whelton of the University of South Alabama led this project. Ten homes were identified through assistance with local nonprofit organizations and word of mouth. Eight of the nine counties were represented. The sampling was conducted from February 11 – 18, 2014. Eight of the 10 households reported symptoms such as rash, dizziness, headaches, and nausea, with four of the households seeking medical assistance for symptoms. A complete description of the water testing methods and results can be found in a companion WV TAP report related to the 10 home study (WV TAP 2014). All ten houses' tap water contained 4-MCHM with 90% of the samples measured at less than or equal to 2.2 ppb. The highest level measured was 6.1 ppb. No trends were found between 4-MCHM detection and location within the house or water temperature.

In addition to the ten home samples, the WV TAP team developed analytical methods to detect and measure 4-MCHM and to identify breakdown products. Eurofins Laboratory and ALS Laboratories conducted all the tap water characterizations for the ten homes. They adapted EPA Method 3510 (US EPA 1996) for the extraction and EPA Method 8720D (US EPA 2007) for the chemical analysis. Eurofins was able to analyze the samples with a method detection level of 0.5 ppb and a method reporting level of 1.0 ppb; these levels were lower than the lowest attained by any other laboratory in the US. The laboratories carefully evaluated the results of the GCMS analyses to determine if any possible breakdown compounds were present in the samples. No breakdown products were observed. No PPH was detected in any of the ten house's water samples; 4-MCHM was observed in all ten homes sampled. Sampling done by the WV TAP team demonstrated that as of March 22, 2014 low levels of 4-MCHM were still present in the finished water produced by the West Virginia American Water (WVAW) treatment plant. Subsequent sampling performed by WVAW showed that MCHM was desorbing from the granular activated carbon (GAC). The team noted that all of the sample results and analyses are posted on the WV TAP website (http://www.wvtapprogram.com) and that in the coming weeks they would be finalizing a design for a larger home study. They anticipated delivering their final report to the State of West Virginia by May 15 and it would include recommendations for short- and long-term activities.

Clarifying Questions from the Panel

Panel members asked the presenters clarifying questions regarding their presentations and the WV TAP program.

Question 1. How confident is Eurofins on identification of all the compounds contained in crude MCHM in the environmental samples?

Dr. McGuire responded that Eurofins and Mel Suffet's laboratory at UCLA each analyzed the crude MCHM and tentatively identified the constituents as compared to what was listed in the Material Safety Data Sheets (MSDS). The identifications were made from library search results generated on the GC/MS systems used for the analysis, but not confirmed with the analysis of known, independent standards. Only the two isomers of MCHM (4-methylcyclohexane methanol) were confirmed with analysis of an independent standard material. Additional peaks were observed in the chromatograms for all the samples taken in the 10-home samples. Initially these peaks were considered candidates for breakdown compounds that might have been caused by treatment of the drinking water with chlorine and with potassium permanganate. Detailed analysis demonstrated that all of the extraneous peaks were results of the breakdown of surrogates added to the samples as part of the laboratory quality control for analyzing for the constituents of the crude MCHM. One particularly confusing tentatively identified compound was finally tracked down to a reaction with a preservative in methylene chloride.

Question 2. The 10-home study did not find any PPH in the household water. Is there any in the distribution system?

Mr. Rosen stated that two samples collected by the West Virginia National Guard and analyzed at REIC laboratories were positive for PPH on January 10th at concentrations of 10 and 11 ppb in the finished water from WVAW. There were very few other samples taken throughout the water system supplied by WVAW where PPH was detected above the method reporting limit of 10 ppb.

Question 3. How many days were the water samples held before the analysis was done and how many follow up samples?

Dr. Whelton responded water samples were collected and shipped daily to the designated laboratory that night. Water samples then underwent analysis within 24 hours. The holding times for all samples were 7 days and all sample analyses were completed within the designated hold times. Some samples were broken in shipping.

Question 4. It is thought that crude MCHM has another constituent that might contribute to the sharp odor, but this constituent is a small percentage of the crude MCHM and too low to detect in the homes that were sampled. How would such a low concentration of the minor component affect the odor of crude MCHM?

Dr. McGuire answered that even if the minor component thought to cause the sharp odor characteristic (cyclohexanemethanol) is in low part per trillion concentrations, it could still affect the odor of crude MCHM.

Question 5. There are CDC documents that describe the 1 ppm screening value. Is there any document describing how the West Virginia 10 ppb level was derived?

Dr. Adams explained that reference to the state's 10 ppb level is found in Governor Tomblin's proclamation of February 28, 2014 (Tomblin, 2014), wherein the state established a more stringent testing threshold of 10 ppb. The proclamation does not explain how this screening level was reached.

Question 6. Appendix M mentions an interagency review of the CDC work, is there a report or documentation of this review that we can use?

Dr. Adams indicated that previously Dr. Kapil of the CDC had told him that there was no report issued by the interagency panel. Additionally, the screening level and its basis reported by the CDC were developed by consensus and vetted within the interagency panel. The interagency panel included the National Institute of Environmental Health Sciences (NIEHS), the National Toxicology Program (NTP), the National Library of Medicine (NLM), the US Environmental Protection Agency (US EPA), and CDC/ATSDR (Agency for Toxic Substances and Disease Registry).

Question 7. – Has there been any central collection or synthesis of public health complaints?

Dr. Whelton explained that he was aware that various groups, including the poison control center, the WV Bureau for Public Health, local emergency departments, and the Kanawha-Charleston Health Department had collected data, but he was not aware of any central collection or any group synthesizing the data. Dr. Rahul Gupta, Director of the Kanawha-Charleston Health Department, provided data from their department for use by the WV TAP and the expert panel. The Kanawha-Charleston Health Department had conducted syndromic surveillance in the two largest counties affected (Kanawha and Putnam). The Health Department shared a description of its work and a summary of results for the panel to use (see Appendix E). The Kanawha-Charleston Health Department collected and compiled data on "frequency of illnesses with a specified set of clinical features not identified with a specific diagnosis" from ten sentinel multi-provider and multi-location medical practices, following standard practice and international and national protocols. These ten providers reported information on more than 200 patients who sought medical attention and who "presented with self-reported symptoms related to exposure to MCHM" with onset after January 9, 2014. The list of symptoms reported included multisystem symptoms (respiratory, digestive, integumentary [skin], neurological); respiratory: cough, sore throat; digestive: nausea, vomiting, diarrhea; skin: rash, skin irritation; neurological: Headache; and "other symptoms" for symptoms that had not been defined. Some patients reported multiple symptoms (e.g., rash, nausea, etc.). The providers did not report names, addresses or other identifying information on the patients beyond gender and age. Graphs created by the Kanawha-Charleston Health Department showed the number of patients by date of symptom onset and of number of illnesses for each self-reported syndrome.

Panel members observed that following the initial spike of symptoms after the contamination event, a further spike in reported symptoms occurred, which coincided with the period of system flushing. They

asked whether there were data to tie the reports of symptoms to the areas being flushed at that time. Dr. Whelton explained that there were not data to do that analysis and noted that some people flushed outside their area's assigned time/permission. Dr. Whelton also relayed to the panel his personal experience of having experienced dizziness while witnessing a flushing in a small, poorly ventilated, bathroom on January 17 or 18. The panel also asked whether it was known if the patients were drinking the water at the time of symptoms, Dr. Whelton indicated that there were no additional data available to answer that question.

PANEL DISCUSSION

Available Data

The panel evaluated the available toxicological data on crude and pure MCHM, utilizing the Adams et al. (2014) literature review and associated references. Panel members noted that although additional and more appropriate studies would allow for a more robust risk evaluation, such studies were not available. They identified a few additional references and other resources that they drew upon, including the development of quantitative structure activity relationship (QSAR) information for the various chemicals in the spill. The QSAR results, while preliminary, suggested that the chemicals were not likely to be mutagenic and one panel member thought that none of the chemicals was likely to be more toxic than MCHM. Several panel members mentioned that because of the limited toxicological data available, the use of such QSAR programs and tools (such as the Organisation for Economic Co-operation and Development [OECD] Toolbox) to gain additional insights into the potential toxicity of these chemicals was reasonable.

Methodology

The expert panel members brought a diversity of backgrounds and experience with toxicology and risk assessment from government, university, and non-profit sectors of Europe, Israel, and the US to the meeting. The panel recognized that the CDC used the US Environmental Protection Agency (US EPA) Health Advisory method (as described in Donohue and Lipscomb 2002) to develop their screening levels for MCHM and PPH. They recognized that the method CDC employed was a traditional approach that used reasonable and common assumptions to develop health protective drinking water health advisory levels. The panel drew upon its collective experience to discuss and consider other organizations' methods and approaches that might be suitable for developing such advisories for the Elk River spill. Panel members discussed their experience and knowledge of various organizations' approaches, but used their own personal best scientific judgment to evaluate and develop their opinions and conclusions for this expert panel.

Several panel members explained how their organizations would approach calculation of a short-term health advisory. All described a similar basic approach, which includes the identification of a point of departure in the dose-response relationship for toxicity and division by uncertainty (safety) factors

(UFs). UFs reflect both variability in biological response between species and within humans, and the lack of knowledge of the toxicity of the chemicals being assessed. Differences in the approaches were seen with regard to the preferred duration of experimental studies, conversion of intermittent dosing to a continuous dose, dosimetric adjustment for species differences, use of a relative source contribution or water ingestion allocation factor with short-term advisories, and selection of the most sensitive (or most exposed) receptor. These differences reflect differences in professional judgment and consideration of more recently adopted approaches, including technical guidance provided by the US EPA, that further refine the basic approach. Key differences in approaches from the United Kingdom (UK), Israel, and Minnesota were discussed.

When providing advice to water companies, the National Centre for Environmental Toxicology (NCET) in the UK prefers to use longer duration studies where available to provide additional protection and precaution. NCET generally uses standard 10-fold uncertainty factors and generally follows the body weights and consumption values for adults and children as used by the World Health Organization (WHO) (WHO, 2011). For spill situations such as the Elk River, they would use the same water consumption and body weight for a child as the US EPA 1- and 10-day health advisory method. NCET would also include a water allocation factor of 50% to account for other routes of exposure.

In Israel there is no specific policy regarding the methodological procedures for determining the advisory level for compounds without existing international reference levels for drinking water thresholds. In cases of water source contamination, the Israeli Ministry of Health would seek an international drinking water threshold-reference or published drinking water threshold from a western country. Any contaminated water source would be closed until the drinking water threshold was achieved. When there is no known threshold, the water source would remain closed until a complete elimination is achieved. In an event where closing the water source is not an option, Israel would use the same traditional and widely accepted methods that were used by the CDC to develop a threshold value for the situation.

The Minnesota Department of Health (MDH) developed risk assessment guidance in 2008 for its health risk assessment program (MDH 2008). These risk assessment methods incorporate recent enhancements for the derivation of toxicity values, much of which comes from guidance issued by the US EPA, including use of dosimetric adjustments. Timing and duration of exposure are carefully considered by Minnesota in deriving reference doses (RfDs) for multiple durations, as well as life stage sensitivity. A panelist explained that the MDH methods have incorporated recently updated recommendations from US EPA that differ in several ways from the 2002 US EPA Health Advisory guidance (i.e., Donohue and Lipscomb 2002). A panelist explained that the differences in methodology, applicable to MCHM, are focused in five areas: (1) the acute and short-term duration receptor of first consideration, when relevant, is the most highly exposed on a water intake per body weight basis (a 1-3 month old formula-fed infant [based on EPA Exposure Factors Handbook (US EPA 2011)]); (2) adjustment of the experimental dose by 5/7 because the animals were only given the MCHM 5 days per week; (3) calculation of a human equivalent dose/concentration by adjusting the animal body weight by a default factor of body weight scaled to the ¾ power; (4) refinement of the uncertainty factor for interspecies adjustment (UF_A) to account for the scaling done in #3; and, (5) consideration of a relative

source contribution to account for other chemical exposures that occur beyond the ingestion of drinking water containing the subject chemical.

Another panelist asked if the MDH methods would be applied to spill situations. The first panelist noted that the MDH's risk assessment methods comprise multiple durations, including shorter-term exposures such as this, and one of the strengths in developing multi-duration guidance is that it can be applied to a wider range of scenarios. He noted that the duration of the 4-week MCHM study fit well with the MDH short-term duration methodology. A panelist asked if US EPA was aware of Minnesota's methodology. The first panelist explained that the MDH methods are based on current US EPA technical guidance, and have their foundation in published US EPA-based technical guidance documentation.

The panel discussed the differences in the MDH methodology and the US EPA Health Advisory approach and that the implications of these alternatives on a short-term health advisory would be to lower the concentration. Because the MDH methods incorporate an adjustment of the animal dose to a human equivalent dose (HED), they also use a more refined approach for the interspecies uncertainty factor for animal to human extrapolation (UF_A) that breaks the UF into two components to adjust for toxicokinetic difference and toxicodynamic differences. The panel discussed that this type of adjustment is largely based on the work of Dr. Andy Renwick and the International Programme on Chemical Safety (IPCS, 2005). MDH has adopted US EPA guidance (US EPA 2011) for using body-weight scaling factors, called dosimetry adjustment factors, in the absence of study-specific time-weighted average animal weights to derive the HED. As the HED is meant to account for the toxicokinetic extrapolation from animals to humans, the UF_A is reduced to 3, with the remainder left to account for toxicodynamic uncertainty in the absence of chemical-specific information. MDH methods are consistent in this approach with the US EPA (US EPA 1988). Other groups apportion this uncertainty factor slightly differently. For example, the IPCS would use a default factor of 4.0 for kinetics and 2.5 for dynamics (IPCS, 2005), rather than the two factors of 3 used by MDH and US EPA.

Charge Question 1: MCHM

The expert panel was provided with a summary of the available health effects data (Adams et al., 2014) as well as copies of the studies and references, prior to the meeting. They used a number of charge questions to help focus their review and discussions (see Appendix B).

Charge Question 1 asked the panel to evaluate and discuss the data and information currently available on crude MCHM, along with the screening levels reported by the State of West Virginia and the US Centers for Disease Control and Prevention (CDC):

- Given the current knowledge, what would be an appropriate screening level for MCHM in drinking water? In your expert opinion, based on the data that are available, do you think that the screening levels are appropriate for the intended uses of the water?
- Discuss the scientific uncertainties and what additional data, analyses, or studies might reduce uncertainty and provide greater confidence.

The panel discussion and conclusions on MCHM are summarized below.

Selection of Study and Point of Departure

The panel reviewed the available studies on crude and pure MCHM (see Adams et al. 2014 for a summary of the literature). They recognized that there were limited data for crude MCHM and agreed with the judgment of CDC that the 4-week oral study in rats with pure MCHM (Eastman, 1990) was the most appropriate study available to establish a short-term health advisory.

The following is a description of this study from the Eastman study report (Eastman, 1990):

> "Groups of two male and two female rats were given doses of 200, 400, or 800 mg/kg/day of 4-methylcyclohexane methanol in corn oil for five days as part of a probe study conducted to establish dose levels for the four-week toxicity study. Rats dosed with 800 mg/kg showed signs of narcosis resulting in decreased activity levels (one male and two females) and ataxia (one female). One of the female rats was subsequently euthanatized. One of the 400 mg/kg/day females had decreased activity on Days 2 and 3 of the study. The remaining animals did not exhibit clinical abnormalities related to exposure to the test article. Dose levels of 0, 25, 100, and 400 mg/kg/day were chosen for the four-week study based on these results.
>
> In the four-week study, the test article was administered five days per week by gavage in corn oil to groups of five male and five female rats. No mortality was observed during this study. Minimal reductions in body weight growth were present for both male and female rats given the high-dose of the test article. These differences were not statistically significant. At lower dose levels, no consistent effect was noted. Males given the lower doses weighed slightly less than their control group while females weighed slightly more. Feed consumption was unaffected by administration of the test material.
>
> Sialorrhea after dose administration occurred frequently in the 400 mg/kg male and female dose groups from Days 14 to 28. Transient depression of activity occurred in one 400 mg/kg female animal on Day 3 of the study. These were the only two treatment-related clinical observations noted.
>
> Hematologic changes indicative of minimal anemia were observed in the 400 mg/kg female group. These changes included a significantly decreased mean red blood cell count relative to the control group, and lower mean values for hemoglobin and hematocrit. In the absence of evidence of increased red blood cell destruction or turnover, these results suggest an interference with erythropoiesis rather than a direct effect on circulating red blood cells. Male and female rats from the 400 mg/kg dose group had significant increases in mean serum creatinine levels relative to their respective control groups, although the differences were not clearly of biological significance as urea nitrogen levels were not similarly increased. Microscopic examination of the kidneys of the 400 mg/kg animals revealed scattered areas of degeneration of the proximal convoluted tubules in 2 out of 5 animals of each sex. While mean relative kidney

weights of all male treatment groups were statistically significantly heavier than their control group, the differences did not fit a dose-related pattern.

Male rats from the 400 mg/kg dose group had significantly higher mean serum aspartate transaminase (AST) and sorbitol dehydrogenase (SDH) levels when compared to their control group. While the high-dose female group did not exhibit similar increases, one of the high-dose females did have an elevated SDH level and the mean relative liver weight for the female high-dose group was statistically significantly increased at the 400 mg/kg dose level. Microscopic examination of the livers from the 400 mg/kg animals of both sexes revealed increased severity and wider distribution of chronic focal inflammation in three males and two females when they were compared to their control groups.

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 subacute toxicity study was 100 mg/kg/day."

Panel members noted that the study used an appropriate OECD method and was conducted under Good Laboratory Practice (GLP).

The panel agreed that a 4-week rodent study was of a reasonable duration to use for deriving a short-term health advisory. One member noted that in his organization in the UK a longer duration study would be used if available to be more conservative; however, in the absence of a longer study (and this is often the case with uncommon chemical contaminants), the use of this study with relevant UFs would be appropriate. Another panelist explained that the 1- and 10-day health advisories would fall under acute and short-term durations, respectively, as outlined by MDH multi-duration methods. MDH would derive acute guidance from a 1-day study and short-term guidance from a multiple dose study lasting longer than 1 day and up to 30 days. In the absence of an appropriate acute study, acute guidance would not be derived. However, if acceptable short-term studies were available, then short-term guidance could be developed. The inclusion of reproductive/developmental studies is preferred for deriving health-protective guidance for all durations, as these types of studies assess life-stage sensitivity. In the case where reproductive/developmental studies are not available, but a study conforming to the short-term duration is available and of sufficient quality to derive guidance, a 10x database uncertainty factor (UF_D) would be applied to the point of departure derived from the available study. The use of this factor is consistent with that used by the CDC.

The Eastman 4-week study was conducted using oral gavage as the route of MCHM administration to the animals. Panel members noted that a study that administered MCHM to the test animals in drinking water would be preferable to gavage dosing for use in setting a drinking water advisory level. In gavage dosing studies, the full daily amount of the chemical is put in the animal's stomach at one time through a gastric tube. One panel member noted that gavage administration often results in higher acute toxicity due to the bolus dosing that causes a higher initial body burden of the test chemical as compared to drinking water studies. Panel members recognized that because of MCHM's strong odor,

conducting drinking water studies could be problematic in that the animals may avoid drinking the water. For MCHM drinking water studies were not available but panel members noted that results of gavage studies are routinely used in risk assessment.

The panel discussed the hematuria findings in the two acute studies (Eastman 1998; Eastman 1999a) with crude MCHM. The first acute study (Eastman 1998) used male and female Sprague-Dawley (SD) rats [SAS:VAF/(SD)] and single gavage doses of 250, 500 or 1000 mg/kg-day. Red discoloration in the urine was reported in some animals and all the animals' urine was then measured for presence of blood using a semi-quantitative dipstick (N-Multistix); all the rats with visible red urine tested positive, as did half of those that did not have visible red urine. The authors considered the positive N-Multistix result in the absence of visible red coloration to indicate "blood in the urine too low to produce visible color changes." (page 6) Eastman conducted a second acute oral study (Eastman 1999) because of problems the laboratory had using the SAS:VAF/(SD) strain of rat (Dyer 2000). The second study used the Crl:CD(SD)IGS BR strain of CD rat. Five female rats were administered a single dose of 500 mg/kg-day. One panel member pointed out that as the animal numbers are low and there was only one dose, this would not be used as a regulatory test, but only as confirmation of a larger study. There were no observations of blood in urine or hematuria in the second study, but the study report did not mention or report on the use of a dipstick to measure blood in the urine directly. Panel members did not think that the second study could rule out hematuria as an effect; they questioned the choice of doses tested and why the more sensitive dip stick was not used. Moreover, the 4-week study showed anemia and kidney lesions at 400 mg/kg-day. Thus, the possible hematuria in the first acute study is consistent with kidney lesions and anemia findings in the 4-week study.

In summary, the panel concluded that, in the absence of other available studies, the oral rat study of 4-week duration was acceptable to use in this assessment for deriving a short-term health advisory for MCHM, although the panel recognized that other organizations might not use this duration study for deriving short-term advisories. The critical effects were anemia in the female animals at 400 mg/kg-day, and histopathology indicating liver and kidney effects in males and females at 400 mg/kg-day. The clinical chemistry findings supported the kidney and liver effects. Two panel members noted that the study report included a substantial discussion of effects seen in the 400 mg/kg-day dose group, but fewer details for the 100 mg/kg-day dose. The panelists thought that this increased the difficulty to critically determine from the study report whether the 100 mg/kg-day is a No Observed Effect Level (NOEL). The panel thought that the individual animal data from the study report would be useful to verify the NOEL of 100 mg/kg-day and asked if these data were available. The receipt of individual experimental animal data from the 4-week study of MCHM would allow confirmation of the study summary and thus afford more confidence in the study's conclusions. A panel member noted that if the individual animal data were available, benchmark dose modeling could be considered to utilize all the dose-response data to better estimate a point of departure. TERA contacted Eastman during the meeting, but was not able to obtain the individual data. The panel concluded that, in the absence of any

further data, the 100 mg/kg-day NOEL from the 4-week oral study in rats with pure MCHM (Eastman, 1990) was the most appropriate to establish a short-term health advisory for MCHM. [2]

Dose Adjustment

The CDC (CDC, 2014a) used the 100 mg/kg-day dose from the Eastman 4-week oral gavage study (Eastman, 1990) as the point of departure for their screening level. The expert panel agreed that this dose was appropriate to use as a starting point, but discussed adjusting it to account for the dosing regimen of 5 days per week. The study used a bolus dose delivered in corn oil by gavage to the experimental animals five days each week with no dosing on the weekends. The study reported a total of 21 doses.

In cases like this, where people are exposed to the chemical in their drinking water for more than a few days, the experimental dose is often adjusted to a continuous dose, to account for anticipated human exposure via drinking water. This is done by multiplying the dose of 100 mg/kg-day by 21 days/29 days, to approximate a continuous dose of 72 mg/kg-day (21 doses multiplied by 100 mg/kg body weight per day, divided by 29 days, equals 72 mg/kg-day). Panel members noted that adjustment to a continuous dose is a common practice and used by the US EPA and others when calculating risk values for lifetime exposures.

Some organizations (e.g., MDH in their health risk assessment program and the US EPA in its Integrated Risk Information System [IRIS] program) would further adjust this dose to calculate a human equivalent dose (HED) or human equivalent concentration (HEC) to account for the toxicokinetic differences between the experimental animal and humans. These adjustments are based on chemical-specific toxicokinetic data and modeling or use generic adjustments based on the animal body weights. For example, using the US EPA (2011a) guidance, dosimetric adjustment factors (e.g., adjusting the animal body weight by a default factor of body weight scaled to the ¾ power) or study specific time-weighted average animal weights could be used to derive an HED. The HED accounts for the toxicokinetic differences between the experimental animal and humans, and therefore the interspecies uncertainty

[2]Post-meeting, the chair of the panel, Dr. Dourson received questions on the panel's selection of critical effect, specifically whether the low dose of 25 mg/kg was a Lowest Observed Adverse Effect Level (LOAEL), based on relative and absolute kidney weights that were statistically significantly greater at the male low dose. Since both relative and absolute changes are normally required for a judgment of adverse effect in the kidney, this dual change appeared to represent an adverse effect. However, the study report noted that:

- higher doses did not show statistically significant increase in absolute kidney weights;
- kidney weights, both relative and absolute, did not show a dose-related trend; and
- these low dose effects did not have matching clinical changes or histopathology, which when compared with organ weight changes, are more definitive.

Toxicology studies often find various effects that are statistically significant at the 5% level, since many more than 20 tests on different organs and systems are monitored. We expect at least 1 in 20 endpoints to show statistically significant results due to chance alone, that is, such results are strictly artifacts of the testing (1/20 = .05 = 5%). Furthermore, experimental animals sometimes adapt to the exposure by specifically increasing the size of the liver and kidney to handle the extra metabolism work that results in elimination and excretion of the chemical. Moreover, the hallmark of adversity is dose- related responses, which did not happen with the kidney weights. The judgment of many, if not all, board certified toxicologists would be that these kidney weight effects at the low dose are either due to chance or due to adaptation.

factor for extrapolation from animals to humans (UF_A) is reduced from 10 to 3 to reflect the remaining uncertainties in toxicodynamics.

In contrast, the CDC used a value of 10 for the UF_A in derivation of their MCHM screening value (CDC 2014a). Such a 10-fold default uncertainty factor is traditionally used by most organizations for interspecies extrapolation. Some panel members noted that groups they work with would use the same approach as CDC for a short-term exposure value. The panel stated that while the CDC approach is traditional and not incorrect, the newer practices mentioned above, specifically, a dosimetric adjustment for the toxicokinetic portion of the UF_A, could also be considered (see Uncertainty Factor discussion below).

Uncertainty Factors

The panel agreed that the 100 mg/kg-day adjusted for the dosing schedule of 21 doses in 29 days (72 mg/kg-day) was the appropriate point of departure to calculate a short-term advisory for MCHM. They agreed that 72 mg/kg-day should then be divided by a 1000-fold uncertainty factor to estimate a short-term reference dose (RfD) of 0.07 mg/kg-day (0.072 rounded to one significant figure for 0.07). This factor consisted of a factor of 10 for interspecies adjustment for extrapolation from experimental animals to humans (UF_A), another 10 for intraspecies adjustment for within human variability in susceptibility (UF_H) and a factor of 10 to account for data deficiencies for an incomplete database that lacked developmental and reproductive toxicology studies and a second species repeat-dose study that monitored systemic effects (UF_D).

The use of a dosimetrically adjusted UF_A would yield a short term RfD of 0.06 or 0.07 mg/kg-day, depending on the method chosen to develop the adjusted UF_A (either the US EPA method used by the Minnesota Department of Health or the IPCS, respectively). These alternative approaches would reduce the toxicokinetic portion of the UFA, but would also lower the POD based on species body weight ratios. Thus, the net effect of these alternatives yields only a slight difference in the short-term reference dose.

Water Consumption

The CDC followed the US EPA Health Advisory method for one and ten-day advisories, with the use of 10 kg for body (approximately 22 pounds) and water consumption of 1 liter/day (approximately one quart). Using these values for a child results in a lower health advisory (more health protective) than if the value were based upon adult weight and water consumption values. The panel recognized that these are common assumptions and represent the high end of the range for a one-year-old child's drinking water intake (US EPA 2011b).

The panel discussed which life stage or subpopulation was most sensitive to MCHM. Panel members noted a lack of toxicological data for MCHM that could provide evidence that a particular life stage is more sensitive or susceptible to adverse effects from exposure to MCHM than other life stages. The rest of the panel agreed. When a most sensitive life stage cannot be identified, the most exposed relevant life stage is often selected for the duration of interest; that is the life-stage specific water intake rates need to match with the duration of the advisory. A panel member noted that on a drinking water intake

per body weight basis, the 1-3 month old infant being fed infant formula made with tap water has a higher consumption per body weight than the 1-year-old infant consumption used by the CDC. Water intake data have been published by US EPA since the 2002 Health Advisory framework was published, and can be found in their Exposure Factors Handbook (US EPA 2011b). These data can be used to match or calculate the appropriate water intake to the duration of interest. For instance, the MDH would consider the formula-fed infant to be the most exposed in the acute (1-day) and short-term (up to 30 days) exposure durations. For a longer duration (>30 days to <10% of lifespan) a young child's time-weighted average intake calculated from the US EPA water intake values from birth to 8 years of age would be used and for a lifetime duration guidance, a time-weighted average from birth to approximately 70 years of age would be used. The panel agreed that, lacking toxicological information on which life stage would be most sensitive to MCHM, consumption for the most exposed relevant life stage should be used. The panel chose to use a consumption rate of 0.285 liters of water per kg of body weight per day. This represents the 95th percentile of water intake for formula-fed infants (see Table Ref 3-19 on page 3-40 of US EPA, 2011b).

Routes of Exposure

People in the affected area have been exposed to MCHM through their community water supply. This water is used for multiple purposes, including direct ingestion from drinking and through foods prepared with water; along with additional routes of exposure such as bathing, brushing teeth, and household uses. People are exposed to the contaminated water through direct ingestion, but also on the skin, and probably through inhalation during showering. The panel discussed whether and how these other routes of exposure could be considered in setting a short-term health advisory.

The information provided by Dr. Gupta and the Kanawha-Charleston Health Department on the frequency of self-reported symptoms related to exposure to MCHM included reports of skin irritation and rashes. The panel noted these general symptoms were not specifically attributed to the contaminated water, but the symptoms appeared to correspond with the first days of the incident and again during the time when water systems in the affected homes were being flushed. The surveillance data, which listed respiratory symptoms, along with Dr. Whelton's reported experience of dizziness while flushing a home's hot water system, led the panel to conclude that inhalation exposures might also be of concern. One panel member noted that in his experience, flushing of water systems is sometimes accompanied by consumer complaints on water quality and in some cases, people link skin irritation to poor water quality. Another panelist noted that the chemicals in crude MCHM are clearly volatile, and their physical-chemical properties can allow them to escape from water and enter the air. Typically, this occurs to the greatest extent when water is heated (e.g., in the home, from cooking or running the dishwater) or sprayed (e.g., during showering). Consequently, household use of contaminated water could result in inhalation exposure in addition to ingestion and dermal exposure. However, without a better understanding of air concentrations of MCHM in homes and the concentrations in air that cause effects, it is difficult to relate inhalation exposure to specific consumer complaints.

The animal toxicological studies showed dermal and eye irritation for both crude and pure MCHM at all concentrations tested, although these concentrations were generally high and the skins of the experimental animals were generally occluded. After additional discussion, the panel agreed that the short-term advisory level should consider potential dermal and inhalation effects from exposure to the contaminated water to the extent possible.

The panel discussed approaches that are used by other agencies and organizations to account for other exposures beyond drinking the contaminated water. A relative source contribution (RSC) is commonly used in risk assessment to address potential exposure from sources and pathways other than ingestion of drinking water. For example, MDH describes the relative source contribution, or RSC, as "a factor used in drinking water risk assessment to allocate only a portion of the RfD to exposure from ingestion of water, and reserves the remainder of the RfD for other exposures, such as exposures from non-ingestion routes of exposure to water (e.g., inhalation of volatilized chemicals, dermal absorption) as well as exposures via other contaminated media such as food, air, and soil." (MDH, 2008)

The US EPA in its drinking water health advisory program also uses an RSC to adjust for other sources and pathways of exposure to the chemical. A default value of 0.2 is used in the absence of sufficient data to the contrary for the lifetime advisory; but the RSC concept is not applied to the calculation of the one day, 10-day, or longer-term drinking water health advisories (Donohue and Lipscomb, 2002). The 0.2 RSC default adjustment assumes that only 20% of a person's exposure to the chemical of interest comes from drinking water and 80% comes from other sources. US EPA guidance on relative source contributions is found in the Ambient Water Quality Program guidance, which contains a decision tree for determining the RSC allotment (20, 50, or 80%) to be used (US EPA, 2000a). The percentage is dependent upon the availability of exposure data to identify and quantify other sources of exposure. In the case of MCHM, there are very limited uses of the chemical, and the potential for people to be exposed to MCHM from sources other than their water supply, such as foods, is not likely.

In the UK, advice to water companies would contain an "allocation to water" of 100% for a one-day exposure, and 50% would be used for a seven-day exposure period. For longer exposure periods (on the order of months rather than years), when there are little data on other sources, an allocation of 50% would also be used. This factor accounts for other sources mainly and other routes of exposure where relevant.

Other authoritative bodies recommend a 50% reduction in the drinking water advisory level as a protective "rule of thumb" to address exposures from a contaminated water source that are other than direct consumption of water. For example, the Superfund program in US EPA Region IV (US EPA, 2014) recommends that dermal and inhalation exposure to volatile chemicals in water while showering is equal to the exposure from direct ingestion, in effect using a factor of 0.5. The logic is that exposure through other exposure pathways not captured from the oral dosing studies (exposures such as showering and bathing) need to be considered in deriving acceptable water concentrations. Although there are limited data, work on volatile chemicals such as chloroform (which is a disinfectant by-product), indicate that uptake of a chemical present in drinking water could double (or more) when inhalation as well as ingestion is considered (WHO, 2004).

A panel member explained that unless the chemical was extremely volatile, or there were data to indicate otherwise, MDH would use a factor of 0.5 for other sources of exposure for the bottle-fed infant scenario. Even if exposure is from a single source (e.g., water), there are other routes of exposure to be considered that in total should not exceed the reference dose established when combined with exposure from ingestion of drinking water. When MDH bases an advisory value on the formula-fed infant, the factor of 0.5 is used as a default value based on the narrow range of environments young infants encounter in the first few months of life. This default of 0.5 RSC for 1-3 month old formula-fed infant is only valid for acute and short-term guidance, for this life stage is very short and therefore the exposure assumption is only relevant to those shorter durations. For longer exposure durations, MDH uses a time-weighted average or adult water intake and the default RSC is 0.2, based on US EPA guidance unless exposure data are available to refine the RSC. Note that a default factor of 0.5 by MDH when using an infant exposure scenario is the same as suggested by US EPA's Superfund guidance.

The panel recognized that different groups have different approaches to adjust short-term health advisories to account for other routes and/or sources of exposure. They range from no adjustment as in the case of the CDC health advisory utilizing US EPA Health Advisory methods, up to reducing the advisory level by up to 80% (multiply by an RSC of 0.2 or divide by a factor of 5). The panel thought that since MCHM can volatilize and surveillance data of Dr. Gupta and the Kanawha-Charleston Health Department indicated that dermal and inhalation exposures to the contaminated water may be having effects, the use of a 0.5 adjustment was reasonable to apply to this situation. A factor other than 0.5 was not selected, since non-water sources of contamination are not expected, and specific data do not exist to inform selection of an alternate RSC. Thus, the panel recommended that a 50% adjustment (i.e., a factor of 0.5) be used for sources and exposures of MCHM from other water uses.

Summary of Calculation of MCHM Short-Term Health Advisory

The panel recommended a short-term health advisory of 120 ppb (120 µg/L) for MCHM. This value was recommended for public health use with the 2014 Elk River spill and the subsequent contamination of the local water supply. The advisory is based on the following calculations:

- Use the No Observed Effect Level (NOEL) of 100 mg/kg-day from the 4 week study of MCHM dated April 3, 1990 by Eastman Kodak (Eastman, 1990).
- Adjust this NOEL to 72 mg/kg-day by multiplying by a factor of 21 days/29 days (0.72) to account for the fact that the rats were only dosed for 5 days per week.
- Divide this adjusted NOEL by a 1000-fold uncertainty factor to estimate a short-term reference dose of 0.07 mg/kg-day (rounded from 0.072); this factor consists of factors of 10 for interspecies adjustment, intraspecies adjustment, and database deficiencies (i.e., missing developmental and reproductive toxicology studies and a second species repeat dose study monitoring systemic toxicity).
- Divide this short-term reference dose by consumption of 0.285 liters of water per kg of body weight per day (US EPA 2011b), representing the 95th percentile of water intake for formula-fed infants (the most exposed population); and then multiply this by 0.5 (RSC) to allow for other possible sources and routes of exposure, such as dermal and inhalation.

- The resulting short-term health advisory is 120 ppb (rounded to two significant digits).

The panel briefly discussed whether the short-term health advisories constituted a safe level of exposure. The majority of the panel expressed agreement with using the term "safe" for the short-term health advisories the panel derived for use in this situation. However, one member preferred to not use "safe," but rather to indicate that the advisories are at levels "not likely to be of concern to human health including the most sensitive individuals" as is used in advice to water companies in the UK. The panel agreed that both of these expressed the panel's intended meaning that the concentrations in water below this level are without appreciable risk to public health.

Chronic Value for MCHM

Development of a chronic guidance for MCHM was briefly discussed in response to a clarifying question. The development of a lifetime RfD or similar chronic duration toxicity value for MCHM would be difficult at the present time, because the longest duration toxicology study is only 4 weeks. The panel provided some thoughts in response to the question, "Can a chronic screening level be developed based on the available data?" A preliminary assessment could be done by considering the use of an additional uncertainty factor to adjust the study results from a short-term to longer-term exposure. Alternatively, additional longer-term studies could be conducted so that a chronic health advisory can be developed without the need for these additional factors.

Charge Question 2: PPH and DiPPH

Sometime after the spill, it was reported that the tank that leaked crude MCHM contained 88.5% MCHM, 7.3% PPH Stripped basic and 4.2% water (CDC, 2014b). According to the CDC (2014b) the PPH Stripped basic is primarily DiPPH and PPH. The relative proportions of DiPPH and PPH, and whether there were other ethers present in the tank is not clear, as several commercial products with varying compositions are available. Dr. Whelton explained that PPH was first measured in water treatment plant effluent in January 2014 at a concentration of 11 ppb concentration. No PPH was detected (detection limit of 0.5 ppb) in the 10 houses sampled. CDC developed a short-term screening level of 1200 ppb for PPH and indicated that this level would also be protective for DiPPH.

As noted earlier, the expert panel was provided with a summary of the available health effects data (Adams et al., 2014), as well as copies of the available studies and references, prior to the meeting. They were given a number of charge questions to help focus their discussions and review (see Appendix B). Charge Question 2 asked them to evaluate and discuss the data and information now available on PPH and DiPPH, along with the screening levels reported by the State of West Virginia and the US CDC.

- Given the current knowledge, what would be an appropriate screening level for PPH and DiPPH in drinking water? In your expert opinion, based on the data that are available, do you think that the screening levels are appropriate for the intended uses of the water?
- Discuss the scientific uncertainties and what additional data, analyses, or studies might reduce uncertainty and provide greater confidence.

The panel discussion and conclusions on PPH and DiPPH are summarized below.

Selection of Study and Point of Departure

The panel reviewed the available information on PPH and DiPPH. Panel members identified additional information, including:

- One panel member noted that the 2011 information the manufacturers provided to the European Chemicals Agency (ECHA) for the REACH program can be found on the ECHA website (available at http://echa.europa.eu). He briefly described REACH (Registration, Evaluation and Authorisation of Chemicals) as a European regulation by which all chemicals produced or used in the European Union are registered and, according to tonnage produced per year, a dossier of information (including toxicology) is submitted. This process is ongoing and administered by the ECHA. A dossier was available on the ECHA website for PPH (CAS number 770-35-4), but not for MCHM or DiPPH.
- WV TAP sent a request to Dow and they provided the panel with a copy of Dow Chemical Company's Chemical Safety Report, Substance Name 1-phenoxypropan-2-ol, July 9, 2010 (Dow Chemical 2010-09-07 CSR-PI-5.2.1) during the meeting.
- The interim California REL for PPH (available at http://www.arb.ca.gov/consprod/regact/2010ra/pph770354.pdf) was also identified and provided to the panel.

Oral toxicological data on PPH included acute studies and *in vitro* and *in vivo* genetic toxicity tests, as well as several key studies that the panel evaluated

- A 90-day drinking water study (and 28-day range finding study) in rats (ECHA, 2014a)
- A two-generation study drinking water study in rats (ECHA, 2014b)
- Prenatal developmental toxicity studies using gavage with rats (ECHA, 2014c) and rabbits (ECHA, 2014d)

Details of these studies, which all used OECD test guidelines and were conducted under GLP, are found in various reports. An OECD document on PPH (OECD 2006) describes much of the data; however, the SIDS document does not include a description of the study in rats that was used by CDC to derive their screening value. This key study (ECHA, 2014c) is included in the REACH submission on PPH, which the panel accessed during the meeting for additional details. Full study reports for the key studies noted above were not available for the panel to review but they utilized the secondary sources including the OECD document and the REACH information found on the ECHA website.

The CDC used results of a rat oral gavage developmental study (ECHA, 2014c) to derive their screening level for PPH. Wister rats (25/sex/dose) were gavaged with PPH emulsified in 0.5% Tylose to 0, 40, 160, and 640 mg/kg-day for 7 days a week on days 6-19 *post coitum*. Details about this study and results are found in the REACH information on the ECHA website. Overt signs of maternal toxicity (reduced food intake and body weight) were seen at the 160 mg/kg-day dose level; the next lowest dose of 40 mg/kg-day was the maternal NOAEL. Fetuses from dams receiving 640 mg/kg-day showed developmental

toxicity (reduced fetal weight and increases in skeletal variations); the next lowest dose of 160 mg/kg-day was the NOAEL for prenatal developmental toxicity. "No substance-induced teratogenicity was seen up to 640 mg/kg per day. Thus, prenatal toxicity was seen at a dose that was severely toxic to the dams. No teratogenic effects were noted at any dose." (ECHA, 2014c)

Panel members thought that this study (ECHA, 2014c) used by CDC was of appropriate quality, in that it used an appropriate OECD method (i.e., OECD method 414), was conducted under GLP, and the REACH dossier assigned it a Klimisch score of 1 (reliable without restrictions).

The panel discussed two other studies: a two-generation drinking water study (ECHA, 2014b) and a 90-day drinking water study in rats (ECHA, 2014a). In the two-generation drinking water study (ECHA, 2014b), Wistar rats (25/sex/group) were administered PPH in drinking water for 26 weeks at concentrations of 0, 100, 1000, or 5000 ppm (0, 11.3, 113.9, 477.5 mg/kg-day). The NOAEL was 1000 ppm (113.9 mg/kg-day), based on signs of systemic toxicity in the parental generations (F0 and F1) seen in the next highest dose group, which was the highest tested dose (5000 ppm, 477.5 mg/kg-day). In the 5000 ppm (477.5 mg/kg-day) group observed effects were: decreased water and food consumption, decreased body weight and body weight gain. Gross and histopathology did not see any substance related adverse effects at any dose.

In the 90-day drinking water study (ECHA, 2014a), Wistar rats were continuously administered PPH in drinking water for 90 days at concentrations of 0, 500, 2000, and 6000 ppm (0, 35/46, 146/177, and 429/486 mg/kg-day bw in males/females). The NOAEL in this study was 146 mg/kg-day (2000 ppm group), based on body weight changes in males and discoloration of urine in both males and females seen in the next highest dose group of 6000 ppm (429/486 mg/kg-day bw in males/females), which was the highest dose tested. Panel members noted that both of these additional studies are of high quality and utilized relevant test guidelines and GLP.

Panel members discussed how other groups would approach this risk assessment and examined other available data to evaluate whether even shorter-term studies were available that might be used to calculate a short-term health advisory. The panel did not find any shorter-term studies to use. Panel members noted that the preference in the MDH methodology would be to use the 90-day study for sub-chronic guidance and the 28-day study for short-term guidance (if this range-finding study was of sufficient quality). The UK's NCET would prefer a 90-day or 26-week study as they feel that the longer duration provides additional protection for exposed populations. However, in the absence of such studies, NCET would consider the above studies in their risk assessment.

The panel thought that the no effect levels from each of these three studies (ECHA, 2014a; ECHA, 2014b; ECHA, 2014c) should be considered as potential points of departure to derive a short-term drinking water health advisory. The panel evaluated the calculations and results for each of the studies in order to reach their recommendation for a short-term health advisory for PPH.

Even though the 90-day drinking water NOAEL (146 mg/kg-day) (ECHA, 2014a) is greater than the NOAEL (114 mg/kg-day) identified for maternal toxicity in the 2-generation study (ECHA, 2014b), and also greater than the NOAEL (40 mg/kg-day) identified in the developmental toxicology study used by

CDC), the panel thought that 146 mg/kg-day was the better choice for the point of departure for a number of reasons. The combination of the 146 mg/kg-day experimental no effect level with the appropriate water intake for infants, resulted in the most conservative water guidance value. The 90-day study used a drinking water exposure route that better represented the human exposure scenario under consideration, when compared to the bolus dosing of the lone gavage study. The 160 mg/kg-day (gavage) LOAEL for maternal toxicity in the 2-generation study was just slightly above the panel's selected point of departure (NOAEL of 146 mg/kg-day), but the nature of gavage bolus dosing reduced confidence in using this study when two other drinking water based studies were available, one of which examined maternal toxicity and found no effects at a nearly equivalent dose level. Moreover, the three studies under consideration were all conducted using the same strain of rodent (Wistar rats), increasing the direct comparability of the endpoints and dose levels under consideration. The panel's choice also represented the highest NOAEL that was also below the lowest LOAEL among these studies. In addition, the panel members thought that the variation in NOAELs among these studies appeared to represent more the variation in the choice of doses used in the studies rather than differences in toxicity. Thus, the panel considered the NOAEL of 146 mg/kg-day to be the best estimate of the boundary between effect and no effect when assessing the available studies as a group. As the 90-day study was conducted in young animals, and no direct-dosing neonatal exposure studies were available to assess the sensitivity of very young animals to PPH, the panel used water intake for the relevant and most exposed population, the formula-fed infant. This combination of NOAEL and intake resulted in a lower value than that derived by CDC (based on a pregnant woman's intake rate and the NOAEL from the developmental study).

Dose Adjustment

The experimental doses from the drinking water studies represented a continuous exposure and did not need to be adjusted further.

Uncertainty Factors

In reviewing the CDC calculations for MCHM and PPH, one panel member observed that CDC used a factor of 10 to account for data base deficiencies, or limitations in the database (UF_D), for both MCHM and PPH. For MCHM, CDC explained the 10 for UF_D "for weaknesses in the toxicological database (10X). For example there are no developmental, neonatal, or transplacental studies available" (CDC 2014a). The panel also judged this appropriate for MCHM. For PPH, CDC used the same 1000-fold uncertainty factor, noting use of 10x "to account for weaknesses in the toxicological database" (CDC 2014b). Panel members noted that there were more studies available for PPH and questioned the use of a full 10-fold database deficiency factor (UF_D) for PPH. However, the available information from the CDC did not provide any further details or rationale for the uncertainty factor selections and the panel did not think it would be appropriate for them to speculate on the CDC's rationale.

Several panel members thought that a case could be made to use a smaller UF_D (e.g., 3X) for PPH. The database for PPH was more robust than MCHM and included several repeat dose studies, a range of genotoxicity tests, and developmental and reproductive toxicology studies. Other panel members

agreed. Thus, the panel determined that a UF of 300 would be appropriate to estimate a short-term reference dose for PPH. This factor consisted of multiples of 10 for interspecies adjustment and intraspecies adjustment, and a factor of 3 to account for data deficiencies.

Water Consumption

The CDC used the body weight (75 kg) and water consumption (2.5 L/day) values for a pregnant woman. It is standard practice to use values for a pregnant woman when the critical effect is maternal toxicity and the panel thought that these values would reasonably protect pregnant women. In developing its three alternative options, the panel considered the most appropriate life stage to use for each of the options as described below.

There were more studies available for PPH than MCHM, including the two-generation studies that dosed parents and young animals with drinking water, a gavage study that dosed pregnant animals, and a 90-day study that tested younger animals. The panel did not find data to determine any particular life stage more sensitive, and thought that differences in NOAELs among the studies appeared to be due more to dose selection. As with MCHM, when toxicological data did not provide evidence that a particular life stage was more or less sensitive or susceptible to adverse effects from exposure than other life stages, the life stage that would be most exposed was used as a default for a short-term health advisory; for PPH this would be the formula-fed infant. Similarly to MCHM, and for the same reasons, the panel used the water consumption rate of 0.285 L/day and a relative source contribution, or water allocation, of 0.5 with the formula-fed infant scenario.

Panel members also noted that at the time of the expert panel meeting (March 31, 2014) no PPH was being detected in the water. Dr. Whelton confirmed that the last time PPH was detected in any water samples was two days after the spill and it was at a low level.

Routes of Exposure

For the same reasons as explained above for MCHM, the panel recommended that a 50% adjustment (i.e., a factor of 0.5) be used for sources and exposures of PPH from other water uses.

Summary of Calculation of PPH Short-Term Health Advisory

The panel recommended a short-term health advisory of 880 ppb (880 µg/L) for PPH. This value was recommended for public health protection use with the 2014 Elk River spill and the subsequent contamination of the local water supply.

- Use the No Observed Adverse Effect Level (NOAEL) of 146 mg/kg-day from the 90-day drinking water study (ECHA, 2014a).
- Divide this NOAEL by a 300-fold uncertainty factor to estimate a short-term reference dose of 0.5 mg/kg-day (rounded from 0.487). This factor consisted of multiples of 10 for interspecies adjustment and intraspecies adjustment, and a factor of 3 to account for data deficiencies (i.e., incomplete database, e.g., missing a second repeat dose toxicology study).

- Divide this short-term reference dose of 0.5 mg/kg-day by consumption of 0.285 liters of water per kg of body weight per day, which represented the 95th percentile of water intake for formula-fed infants (the most exposed population); and then multiply this by 0.5 (RSC) to allow for other possible sources and routes of exposure, such as dermal and inhalation. The resulting short-term health advisory for PPH is 880 ppb (rounded to two significant digits).

DiPPH

CDC noted in its document on PPH that, "Very limited specific toxicological information is available for DiPPH at this time. However the LD50 of >2000mg/kg and chemical structure suggest similar or lower toxicity, and the screening value calculated for PPH would also be protective for DiPPH" (CDC 2014b). The panel agreed with CDC and noted that the available manufacturers' information indicated that DiPPH is the major constituent of PPH Stripped. The panelists discussed whether there were sufficient data currently available to estimate a short-term advisory for DiPPH. One panel member noted that the LD50 values for PPH and DiPPH are greater than 2000 mg/kg-day, this was one piece of information to support that they are similar, but not sufficient alone. Others thought that the two are structurally similar and with LD50 values greater than 2000 mg/kg for both chemicals, that it would be appropriate to use the PPH results to estimate a DiPPH value. Other panel members agreed, with the stipulation that the UF_D uncertainty factor should be 10, rather than 3, to reflect the greater uncertainty in the DiPPH database.

The panel recommended a short-term health advisory of 260 ppb (260 µ/L) for DiPPH. This value is recommended for public health protection use with the 2014 Elk River spill and the subsequent contamination of the local water supply.

- Use the No Observed Adverse Effect Level (NOAEL) of 146 mg/kg-day from the 90 day drinking water study of PPH (ECHA, 2014a);

- Divide this NOAEL by a 1000-fold uncertainty factor. This factor consists of multiples of 10 for interspecies adjustment, intraspecies adjustment, and to account for data deficiencies (e.g., missing many studies); then divide by consumption of 0.285 liters of water per kg of body weight per day, which represented the 95th percentile of water intake for formula-fed infants (the most exposed population); then multiply this by 0.5 (RSC) to allow for other possible sources and routes of exposure, such as dermal and inhalation.

- The resulting short-term health advisory for DiPPH is 260 ppb (rounded to two significant digits).

Note that the panel did not develop a short-term reference dose for DiPPH because the assessment was based on the toxicity of PPH.

Charge Question 3: Mixtures

Charge Question 3 addressed the presence of multiple chemicals from the tank that spilled into the Elk River. The panel was asked:

> How should the presence of multiple chemicals in the release to the Elk River (i.e., crude MCHM, PPH and Di-PPH) be considered in the derivation or application of the screening values?

Panel members discussed that the mixture of concern is the contents of the tank that spilled in the river: crude MCHM and PPH Stripped basic. The CDC reported that the tank contents were 88.5 % MCHM, 7.3 % PPH Stripped basic and 4.2 % water. Both crude MCHM and PPH Stripped are commercial products that are mixtures of chemicals and these commercial products may have varying compositions.

Panel members began their discussion by briefly reviewing how chemical mixtures are generally assessed. They noted there is no single approach used by all authorities and groups. The US EPA approach to mixtures risk assessment is found in the US EPA *Guidelines for Health Risk Assessment of Chemical Mixtures* (US EPA 1986 and 2000b). These guidelines describe a commonly accepted approach in the US and elsewhere for assessing risk to humans from chemical mixtures. US EPA (US EPA 1986 and 2000b) recommends first looking for toxicity information on the actual mixture of concern, in the absence of this information, data on similar mixtures are sought. If data on similar mixtures are unavailable, one considers the toxicity of the individual components in the mixture and how the toxicity of the components might interact to affect the toxicity of the mixture. In determining how best to consider the cumulative activity of the individual chemicals in a mixture, the risk assessment scientist considers the individual chemical's mode or mechanism of action as well as any information on interactions among the components.

Data on toxicity of specific chemical mixtures are rarely available and data on sufficiently similar mixtures are often lacking as well. Thus, the most commonly used approach is to assess the potential hazards for each chemical and then sum the hazards after considering potential for interactions in the exposure or toxicity of the chemicals. This process considers any experimental toxicology data on interactions between or among chemicals.

The quantification of MCHM in water is based on pure MCHM (a mixture of cis and trans isomers). The panel noted that there are few or no data on some components in crude MCHM and discussed how one could best address the toxicity of the crude MCHM mixture when it includes components for which there are no toxicity data or risk values. One panelist said that given pure MCHM makes up the bulk of the crude MCHM, he would focus on the toxicity of pure MCHM. Others suggested that a systematic look for information on similarly-structured chemicals might be helpful, although several panelists stated that their informal review of structure-activity-relationships did not suggest unsuspected toxicity.

The panel discussed that in a situation such as this, where toxicity data were not available for the mixture of concern (i.e., the tank contents), nor for a similar mixture, combining the toxicity of the individual components would be a reasonable approach. The panel recommended assuming additivity for the components of the mixture that work on the same mode of action or have similar critical effects.

One panelist explained that the US Superfund approach (US EPA, 2001) to this situation one would need to estimate how much exposure people have to each chemical and identify risk values for each of the chemicals (e.g., "safe" or acceptable levels such as reference doses or tolerable daily intakes). A hazard quotient (HQ) is calculated for each chemical by dividing a person's expected daily exposure to the chemical by the risk value. An HQ of one or less than one indicates the exposure is not likely to be a risk to human health. One then adds together all of the HQs for similar-acting compounds (same mode of action or critical effect). A total HQ equal to or less than one would indicate the total exposure of the chemicals combined is not likely to be a risk to human health. Alternatively, one could add each of the chemical's daily exposures together and compare this total daily dose with the short-term health advisory for MCHM. Again, if the HQ is equal to or less than one, then the exposure is not likely to be a risk to human health. For a mixture of PPH, DiPPH and MCHM, MCHM is the most potent and also makes up a large percentage of the tank contents that spilled. The panel thought that for these chemicals, evaluating the toxicity of the mixture could be approached by a simple additivity of each component toxicity. In the case of crude MCHM, the panel thought that it was reasonable to assume its toxicity would be similar to the toxicity of pure MCHM.

The panel also briefly discussed that there may be other chemicals in the drinking water; perhaps disinfectant by-products that acted on the same toxic endpoint that might need to be considered when using an additivity approach. In addition, it is not known how the spilled chemicals interact with the environment, the water treatment plant, the distribution system, or the plumbing and fixtures in buildings and homes. The panel recommended that research be done to determine the chemical fate and transport of the spilled chemicals of major concern within the treatment plant and water distribution system.

The panel agreed that an appropriate approach to consider the mixture of chemicals in this spill would be to do a constituent-specific analysis and use dose addition following US EPA's mixtures guidelines (US EPA 1986 and 2000b). Surrogates could be chosen for those chemicals without adequate toxicity information, or they could be excluded from the calculation.

Charge Question 4: Multiple Uses of Water

Charge Question 4 addressed people using contaminated water for multiple purposes:

> Residents use water for drinking, bathing, showering, brushing teeth, cooking, baby formula, pets, washing dishes, water plants, etc. Are the reported screening values protective for all potential routes of exposures (i.e., ingestion, dermal and inhalation)? If not, how can these other routes of exposure be addressed?

The panel recognized that people are exposed to the contaminated water in various ways and attempted to account for these additional exposures by including an extra factor (e.g., relative source contribution or water allocation factor) in the calculation of the short-term health advisories discussed in this report. This factor helps account for exposures from contaminated water other than drinking and preparing foods and beverages; these other exposures may include bathing, showering, brushing teeth, washing dishes, and watering plants.

Research and Data Needs

The panel discussed what additional data, analysis, or research might help reduce uncertainty. They identified two research or data needs specifically for MCHM and suggested three other areas where further analysis and research would aid in better understanding the hazard and risk from this spill.

The panel made five recommendations for additional data, analyses, or research:

1. **Undertake research to determine what level of MCHM in water would cause skin irritation in humans**.

   Panel members noted that there were anecdotal reports of dermal symptoms (irritation, rash), which may or may not be attributable to the water. Dermal toxicology studies indicated MCHM is a strong irritant, with a low potential for systemic toxicity (through dermal exposure) and dermal LD50 values are greater than the oral LD50 values. The dermal studies were conducted to identify hazard and not dose-response, and experimental protocols, such as skin occlusion, would not be expected to be part of the human experience. In the experimental animal studies, 100 mg/kg-day was the lowest dose with dermal irritation reported (Eastman, 1999b). The panel recognized that the experimental animal results might be consistent with the surveillance reports. However, a threshold for dermal irritation was not known and the available data were not sufficient to estimate a threshold. The panel recommended that further research be undertaken to determine the potential concentrations of MCHM in water that could cause skin irritation in humans.

2. **Conduct toxicology studies for MCHM in pregnant animals**.

   The panel discussed the types of toxicological studies that were not available for MCHM. The 10-fold uncertainty factor was applied for an incomplete database due to lack of several studies including a two generation reproductive study, two developmental toxicity studies in separate species, a repeat dose toxicity study in a second species, and genotoxicity studies (beyond the Ames test results). The panel was most concerned about the lack of any animal data on developmental toxicity hazard and they recommended that a developmental study in rodents would be useful to evaluate the potential for MCHM to act as a specific developmental toxicant. This could be combined into a two-generation reproductive/developmental toxicity study, if sufficient funds were available. A repeat dose study in a second species was of lesser importance, although one panelist noted that a continuous exposure drinking water-based study would be beneficial. With regard to potential genotoxicity, several panel members ran the chemicals through QSAR programs and they reported that all predictions were negative for genotoxicity. The missing studies are currently covered in the screening level calculation with use of a 10-fold uncertainty factor (UF_H). Availability of an additional developmental/reproductive study could result in a reduction of this UF_D to 3-fold. In addition, further studies may identify a better point of departure (POD), which may also have the impact of changing the short-term health advisory, depending upon the POD and selection of appropriate corresponding UFs.

3. Organize all available data on exposures and health effects (from immediately following the spill) to facilitate the estimation of initial conditions.

The panel members did not have information on what people were actually exposed to in the initial days after the spill. They understood that multiple parties measured concentrations of the chemicals in the river, water plant and finished water. The panel recommended that data be collated and analyzed to better understand and estimate exposure.

In addition, air levels resulting from water use in the home would help the understanding of potential inhalation risks from water usage. Data on inhalation exposure would help refine the evaluation of this exposure route that the panel was only able to address through application of a relative source contribution/water allocation factor.

Multiple parties have collected data related to symptom reports. These should also be collated and all of this data should be analyzed together to better understand exposure and effects.

4. Pending results of #2 and #3, consider the need for long-term health effects study.

The panel recommended in #2 that developmental toxicology studies be conducted with MCHM to determine the potential for effects on the fetus or on development. If these studies show developmental effects that are specific to MCHM and not due to maternal toxicity (#2) and a reliable estimate of exposure can be developed (#3) then the panel would recommend consideration of conducting a longer-term health effects (epidemiology) study.

5. Determine chemical fate and transport within the treatment plant and water distribution system.

The panel discussed reports in the media (published around the time of the expert panel meeting) of MCHM being captured in the water treatment plant's activated carbon filters and the hypothesis that some of the captured chemical may still be washing off the filters and entering the finished water. In addition, panel members understood that it is not known whether the spilled chemicals might interact with other chemicals in the water (e.g., disinfectant chemicals or disinfectant byproducts) or how they might interact with the distribution system pipes and materials, as well as fixtures in the home. The panel recommended additional research be done on chemical fate and transport.

QUESTIONS FROM PUBLIC MEETING OF MARCH 28, 2014

The WV TAP team asked the panel to consider several of the questions raised by members of the public at the March 28 public briefing. The panel briefly discussed these and provided the following thoughts.

- *Will the panel consider health impacts on women and particularly pregnant women?* The panel developed the short-term health advisory levels to be protective for all people, including pregnant women.
- *Can MCHM exposure in steam be tied to headaches or irritated throat?* The panel noted that there are no toxicology data for MCHM that can answer this question directly. The panel reduced the advisory level by half to be protective for the potential exposures of contaminated water from inhalation and skin contact.
- *What about interaction with pharmaceuticals taken for diabetes or sleep apnea*? The panel members do not know of specific information or basis to predict interactions of the contaminated water with pharmaceuticals in the human body. The panel recommended that concerned individuals should consult their physician.
- *Is this stuff going to kill us and at what level? What is the difference between the fear and the actuality?* The panel estimated short-term health advisory levels for MCHM, PPH and DiPPH. Exposures to concentrations in water at or below these levels are without appreciable risk to public health, including sensitive subgroups.
- *Is the water safe for pets?* The panel thought that the safe levels established for people should also be safe for pets. This is because the main experimental studies used for the derivation of the drinking water advisories for people were carried out in rats. Large uncertainty factors were then used to set a much more precautionary level for humans. Therefore, these drinking water advisories will be safe for pets; the pets' response to the chemicals is likely to be similar to the experimental animals.
- *Do the chemicals leach into hard skin vegetables?* The panel did not have specific information to answer this question, but believed that the additional factor of 0.5 for other routes and exposures would protect people from any additional exposures via washing vegetables.
- *Everything is based on the CDC screening level recommendation. We don't even know if that is a valid safety threshold.* The panel reviewed the CDC screening values. The CDC used traditional methods and reasonable assumptions of the US EPA Health Advisory program to develop their screening levels. This expert panel's conclusions are not incompatible with the CDC values; the panel used more refined methods to calculate the short-term advisories, including an adjustment to account for additional routes of exposure (dermal and inhalation).

CONCLUSIONS

The panel reviewed available data for MCHM, PPH, and DiPPH and developed short-term health advisories for each that are appropriate for the intended uses of the water supply. Each of the

screening values was intended to protect all portions of the population, including infants, children and pregnant women. Each value was meant to protect for exposures to the water through direct ingestion, inhalation from showering and household water use, skin exposure and incidental exposures such as brushing teeth.

The panel evaluated the available toxicological data on crude and pure MCHM utilizing the Adams et al. (2014) literature review and associated references. Panel members noted that although additional and more appropriate studies would allow for a more robust risk evaluation, such studies were not available. They identified a few additional references and other resources they drew upon, including the development of QSAR information for the various chemicals in the spill.

The expert panel was made up of independent experts from the US, UK and Israel; they were not constrained to use any particular method. The panel thought that the CDC used traditional methods and reasonable and common assumptions of the US EPA Health Advisory program to develop their screening levels to develop their screening levels. The use of an RSC and 1-3 month old infant intake are not included in the US EPA Health Advisory methodology from 2002. This expert panel's conclusions were not incompatible with the CDC values; however, this panel chose to adjust their advisory levels further to account for additional routes and pathways of exposure (dermal and inhalation). In addition, the panel used intake levels for what it deemed to be the most exposed life stage (i.e., the formula-fed infant). The panel developed these short-term health advisories for public health use with the 2014 Elk River spill and the subsequent contamination of the local water supply.

- The panel recommended a short-term health advisory of 120 ppb (120 µg/L) for MCHM.
- The panel recommended a short-term health advisory of 880 ppb (880 µg/L) for PPH.
- The panel recommends a short-term health advisory of 260 ppb (260 µg/L) for DiPPH.
- The panel derived short-term health advisories for MCHM, PPH and DiPPH.

The MCHM advisory is based upon a 28-day rodent study, and with the appropriate uncertainty factors is applicable for human exposure situations of one day up to approximately 3 months. The PPH and DiPPH advisories are based upon a 90-day rodent study and a formula-fed infant scenario, and therefore they are also appropriate to use in situations from one day up 3 months. Panel members thought that these values may also be useful for longer exposures, but this would entail determination of the most appropriate water intake to match the exposure duration of interest.

The panel's advisories each have two digits of precision. While guidance is often provided to express these advisories at the level of one significant digit, the panel chose to include two digits to aid in the reader following the calculations and understanding the results.

The panel agreed that an appropriate approach to consider the mixture of chemicals in this spill would be to do a constituent-specific analysis and use dose addition following US EPA's mixtures guidelines (US EPA 1986 and 2000b). Surrogates could be chosen for those chemicals without adequate toxicity information, or they could be excluded from the calculation.

The panel discussed the scientific uncertainties and what additional data, analyses, and studies might reduce uncertainty and provide greater confidence. They recommended five areas for further work:

1. Undertake research to determine what level of MCHM in water would cause skin irritation in humans.
2. Conduct toxicology studies for MCHM in pregnant animals.
3. Organize all available data on exposures and health effects (from immediately following the spill) to facilitate the estimation of initial conditions.
4. Pending results of #2 and #3, consider the need for long-term health effects study.
5. Determine chemical fate and transport within the treatment plant and water distribution system.

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APPENDIX A: PANEL BIOGRAPHICAL SKETCHES AND CONFLICT OF INTEREST

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Expert Panel Bios

Dr. Michael Dourson, Toxicology Excellence for Risk Assessment, Cincinnati, Ohio, USA
Since 1995, Dr. Dourson has served as President for Toxicology Excellence for Risk Assessment (TERA). Dr. Dourson will Chair the Expert Panel and has over 30 years experience in toxicology, risk assessment and derivation of risk values. While with the US Environmental Protection Agency (EPA) he chaired the EPA's Reference Dose (RfD) Work Group, was a charter member of the US EPA's Risk Assessment Forum, and chief of the group that helped create the Integrated Risk Information System (IRIS). Dr. Dourson received his Ph.D. in toxicology from the University of Cincinnati and is a Diplomate of the American Board of Toxicology (DABT) and a Fellow of the Academy of Toxicological Sciences. He has served on or chaired many expert panels in the US EPA, Food and Drug Administration (FDA), National Sanitation Foundation International, and independent organizations. He served as President of the American Board of Toxicology and Secretary for the Society for Risk Analysis (SRA), and has published more than 100 papers on risk assessment methods.

Dr. Shai Ezra, Mekorot, Israel National Water Company Ltd, Tel Aviv, Israel
Dr. Ezra is the Director of the Water Security Department at the Water Quality Division of Mekorot. Dr Ezra's department is responsible for optimizing contaminant detection efficiency, and applying advanced online monitoring systems and response strategies in Mekorot's water systems. He is continually engaged in examining and developing state of the art technologies for early warning detection systems. Dr. Ezra received his Ph.D. and M.Sc. from the Geological and Environmental Sciences Department of Ben Gurion University of the Negev, Israel. Dr. Ezra has investigated water quality issues in water distribution systems and has lectured in environmental organic geochemistry. He has published on water contamination issues, including chemical transformation and degradation of organic contaminants in aquifers, and decontamination methods of water pipe systems after contamination events.

Dr. James Jacobus, Minnesota Department of Health, Saint Paul, Minnesota, USA
Dr. James Jacobus is a research scientist and risk assessor in the Health Risk Assessment Unit at the Minnesota Department of Health (MDH) in St. Paul Minnesota. Dr. Jacobus derives multi-duration health-based guidance for drinking water contaminants of special concern. In his position at MDH, Dr. Jacobus has authored or reviewed toxicological assessments on approximately 15 contaminants of emerging concern, evaluating the available toxicity data to derive drinking water guidance values for acute, subchronic and chronic durations and addressing different life stages. Dr. Jacobus has worked as an environmental scientist engaged in the remediation of leaking underground storage tanks and performed basic science research on the genotoxicity of semi-volatile polychlorinated biphenyls and the biological effects of ionizing radiation. He earned his doctorate in human toxicology from the University of Iowa, trained as an NIH T-32 postdoctoral fellow, and holds an adjunct faculty appointment at the University of Minnesota.

Dr. Stephen Roberts, University of Florida, Gainesville, Florida, USA

Dr. Steve Roberts is Director of the Center for Environmental & Human Toxicology at the University of Florida, and is a Professor in the College of Veterinary Medicine, College of Medicine, and the College of Public Health and Health Professions. He received his Ph.D. from the University of Utah, College of Medicine, and subsequently completed a National Institutes of Health (NIH) individual postdoctoral fellowship in pharmacokinetics at SUNY Buffalo. He has previously served on the faculties of the College of Pharmacy at the University of Cincinnati and the College of Medicine at the University of Arkansas for Medical Sciences. Dr. Roberts conducts research in a number of areas of toxicology, including mechanisms of toxicity, toxicokinetics, nanotoxicology, and risk assessment. His research has been funded by several federal agencies, including the National Institutes of Health (NIH), the U.S. Environmental Protection Agency (EPA), and the Department of Defense (DOD). Dr. Roberts currently serves as an advisor to the Florida Department of Environmental Protection and is on the Chemical Assessment Advisory Committee of the Science Advisory Board for the U.S. EPA.

Dr. Paul Rumsby, National Centre for Environmental Toxicology at WRc plc, United Kingdom

Dr. Paul Rumsby is a Principal Toxicologist and Technical Manager of the National Centre for Environmental Toxicology (NCET) at WRc plc (formerly the Water Research Centre), in Swindon, United Kingdom. He received his Ph.D. in biochemical pharmacology from the University of Dundee and is a European Registered Toxicologist (ERT). He serves as the project manager and overseeing scientist for a 24-hour toxicology advisory service and conducts scientific evaluations of data on occupational and environmental chemicals for risk assessment and drinking water monitoring studies on chemicals of regulatory importance. He has conducted reviews of toxicological data for human health risk assessments from drinking water contamination incidents and the setting of short-term guidance values. He has 25 years' laboratory research experience in molecular toxicology and cancer research and is an expert in mechanisms in toxicology including carcinogenesis, mutagenesis, neurotoxicity, and endocrine disruption. Dr. Rumsby has authored numerous peer-reviewed publications on drinking water contaminants.

Conflict of Interest Screening

To facilitate the evaluation of potential conflict of interest (actual and perceived) and bias situations for the peer review candidates, TERA identified a list of *potentially* affected or interested parties and sectors for this peer review. The candidates were asked to consider their financial and other relationships with these parties when completing the conflict of interest questions and to report any relationships they may have with these parties. The candidates were also questioned about current and past activities or interest for the list of chemicals involved.

Potentially Affected or Interested Parties:

- State of West Virginia
- Centers for Disease Control and Prevention
- Freedom Industries
- Eastman Chemical
- DOW Chemical [PPH (one of the chemicals in the Crude MCHM and spilled) is manufactured by DOW, although the source of PPH in the tank is not clear]
- West Virginia American Water
- American Water Works Service Company [Parent company of West Virginia American Water]
- Coal mining industry (including mining, processing, storage, and transport)

Expert Panel:

Michael Dourson is President of TERA. TERA conducts work under contract for government and private sector sponsors on chemicals and risk assessment issues. He has no conflicts of interest for this peer review.

Shai Ezra is the Director of the Water Security Department at the Water Quality Division of Mekorot. He participated in an Israeli delegation to West Virginia hosted by the WV National Guard in January of this year to learn about the spill situation. He has no conflicts of interest for this peer review.

James Jacobus is a research scientist and risk assessor in the Minnesota Department of Health. He has no conflicts of interest for this peer review.

Stephen Roberts is Director of the Center for Environmental & Human Toxicology at the University of Florida, and is a Professor in the College of Veterinary Medicine, College of Medicine, and the College of Public Health and Health Professions. He has no conflicts of interest for this peer review.

Paul Rumsby is a principal toxicologist and technical manager of the National Centre for Environmental Toxicology (NCET) at WRc plc (formerly the Water Research Centre. He has no conflicts of interest for this peer review.

Toxicology Excellence for Risk Assessment (TERA)

TERA evaluates the potential for conflict of interest for each potential new project. The following is a summary of information for this project that TERA is disclosing in the interests of transparency.

TERA has no current financial or other interest with any of the chemicals identified in the spill. In the past, TERA compiled toxicity data and a hazard summary on one of the chemicals, methanol, for the U.S. EPA and organized a letter peer review of methanol toxicology studies for the Methanol Institute. TERA currently has projects with Dow AgroSciences and Dow Corning (a subsidiary, and joint venture, respectively of Dow Chemical) to evaluate chemical toxicity for several chemicals that are not related to this project. TERA has done work in the past for Dow Chemical and Eastman Chemical on other chemical toxicity evaluations, but not on any of these chemicals. TERA assisted the State of West Virginia in organizing a peer panel to conduct a risk assessment and toxicology evaluation of Ammonium, perfluorooctanoate (PFOA) in 2002. None of these projects involved the spill chemicals and the projects are not related in any way to this peer review, and therefore there is no conflict of interest for this peer review or reason for TERA or Dr. Dourson not to be objective in this matter.

APPENDIX B: MEETING MATERIALS

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Fact Sheet on WV TAP Expert Panel

Background

This meeting of an independent expert peer review panel has been organized by Toxicology Excellence for Risk Assessment (TERA*)*. TERA is an independent non-profit organization whose mission is to support the protection of public health by developing, reviewing, and communicating risk assessment values and analyses, improving risk methods through research, and educating risk assessors and managers and the public on risk assessment issues. TERA has organized and conducted peer reviews for private and government sponsors since 1996 (see http://www.tera.org/Peer/index.html for information about TERA's program).

Peer review is an essential part of science– peer review is the evaluation of scientific, work by others working in the same field. Evaluation by a diverse group of independent "peers," provides for a scientifically robust and objective appraisal of the work.

TERA has selected and convened a panel of five experts to review and discuss the available toxicology data and the scientific support for the West Virginia Screening Level established at 10 parts per billion (ppb). The panel will discuss the initial starting value of 1 part per million (1,000 ppb) established by the US CDC and then consider if the additional safety factor applied by the State of West Virginia was protective of public health, based on available data. The panel will identify data gaps and make recommendations for additional studies or analyses that could strengthen the screening level and reduce uncertainty. The expert panel will seek to reach consensus or common agreement on the scientific issues and conclusions.

The panel will draw upon the scientific review document authored by Utah State University Professor Craig Adams. The document can be found on the WV TAP website and is entitled *Health Effects for Chemicals in 2014 West Virginia Chemical Release: Crude MCHM Compounds, PPH and DiPPH. Version 1.5.* The document provides a literature review summarizing toxicity information on the chemicals that were spilled into the Elk River in West Virginia in January 2014 from the Freedom Industries facility.

In the spirit of the Expert Panel's independence and mission, it would not be appropriate for the experts to discuss the subject of this review publically before they deliberate as a group and finalize their report.

Independent Expert Review Panel

The independent peer review panel includes five scientists who have expertise in the key disciplines and areas of concern. Each panelist is a well-respected scientist in his or her field. The panel has training and experience in the various scientific disciplines involved in evaluating the safety of chemicals in water. Collectively, the panel members are experts in toxicology, derivation of screening levels, human health risk assessment, and water contaminants and systems. They have experience in academia, government, research, and non-profit sectors, which will provide a diversity of perspectives in the discussions. TERA questioned each candidate on their relationships with interested parties, to identify

any potential conflicts of interest. TERA was solely responsible for the selection of the panel members. The experts serve as individual scientists and will represent their own personal scientific opinions. They are not representing their companies, agencies, funding organizations, or other entities with which they are associated. Affiliations are for identification purposes only.

- Dr. Michael Dourson, Toxicology Excellence for Risk Assessment, Cincinnati, Ohio USA
- Dr. Shai Ezra, Mekorot, Israel National Water Company Ltd, Tel Aviv, Israel
- Dr. James Jacobus, Minnesota Department of Health, Saint Paul, Minnesota USA
- Dr. Stephen Roberts, University of Florida, Gainesville, Florida USA
- Dr. Paul Rumsby, National Centre for Environmental Toxicology at WRc plc, United Kingdom

Review Package and Charge to Peer Reviewers

In preparation for the meeting, the expert panel reviewed the Adams et al. literature review and pertinent references. TERA provided the panel with a list of key questions (the "charge to peer reviewers") to help focus the discussions. The charge questions are briefly described below:

- Given data now available, what would be appropriate screening levels for MCHM and PPH in drinking water?
- What additional data, analyses, or studies might reduce uncertainty and provide greater confidence?
- How should the presence of multiple chemicals in the release to the Elk River be considered?
- Are the screening values protective for all potential routes of exposures (i.e., ingestion, dermal and inhalation)?
- Please identify any additional scientific issues or questions that the panel should discuss.

Meeting Report

The consensus opinion of the panel as a whole is the valuable result of this expert review. Preliminary conclusions from the panel's discussions will be reported on April 1. TERA will draft a meeting report that summarizes the expert panel's discussions and conclusions, and this report will serve as the record of the peer review. The draft report will be reviewed by the panel members for accuracy and completeness and the final report will be approved by the panel before it is released. The goal is to have the final report complete by the end of April.

Press Conference, April 1, 2014

A press conference to present preliminary conclusions will be held Tuesday, April 1 at West Virginia State University in Institute, West Virginia. Similar to the March 28 public meeting, the Expert Panel press conference will be held in the Ferrell Hall Auditorium. The auditorium, on the 2nd floor of Ferrell Hall, has theatre style audience seating for 400 persons on the lower level and 200 persons in the balcony. The event will begin at 10:00 AM EDT and conclude at approximately 11:00 AM EDT.

TERA
TOXICOLOGY EXCELLENCE FOR RISK ASSESSMENT

WV TAP
WEST VIRGINIA TESTING ASSESSMENT PROJECT

Agenda

Charleston, West Virginia

Monday, March 31, 2014

8:00	**Arrival, coffee**
8:30	**Meeting Convenes**[3]
	Welcome, Ms. Jacqueline Patterson, TERA
	Panel Introductions and Conflict of Interest/Bias Disclosures, Panel
	Meeting Process and Ground Rules, Dr. Michael Dourson, Chair
9:00	**Background**
	WV TAP Team
	Clarifying Questions from the Panel
9:30	**Panel Discussion of Data and Charge Questions**
12:00`	**Lunch (provided)**
1:00	**Panel Discussion of Data and Charge Questions, continued**
5:00	**Meeting Adjourns**

[3] The Chair will call a break mid-morning and mid-afternoon.

Charge Questions

Introduction

The expert panel will review and discuss the available toxicology data and the scientific support for the West Virginia Screening Level established at 10 parts per billion. They will discuss the initial starting value of 1 ppm established by CDC and then consider if the additional safety factor applied by the State of West Virginia is protective of public health, based on the data that are currently available. The panel will identify data gaps and make recommendations for additional studies or analyses that could strengthen the screening level and reduce uncertainty.

The panel will then be asked to consider whether any additional data are available on the chemicals that were released from the tank: pure-MCHM and the chemicals found in crude-MCHM, PPH, and Di-PPH. The Review Package includes the literature available to both the State of West Virginia and the CDC, as well as a literature review put together by Craig Adams and related references.

1. Evaluate and discuss the data and information now available on crude-MCHM, along with the screening levels reported by the State of West Virginia and the US Centers for Disease Control (CDC).
    - Given the current knowledge, what would be an appropriate screening level for MCHM in drinking water? In your expert opinion, based on the data that are available, do you think that the screening levels are appropriate for the intended uses of the water?
    - Discuss the scientific uncertainties and what additional data, analyses, or studies might reduce uncertainty and provide greater confidence.

2. Evaluate and discuss the data and information now available on PPH and DiPPH, along with the screening levels reported by the State of West Virginia and the US Centers for Disease Control (CDC).
    - Given the current knowledge, what would be appropriate screening levels for PPH and Di-PPH in drinking water? In your expert opinion, based on the data that are available, do you think that the screening levels are appropriate for the intended uses of the water?
    - Discuss the scientific uncertainties and what additional data, analyses, or studies might reduce uncertainty and provide greater confidence.

3. How should the presence of multiple chemicals in the release to the Elk River (i.e., crude-MCHM, PPH and Di-PPH) be considered in the derivation or application of the screening values?

4. Residents use water for drinking, bathing, showering, brushing teeth, cooking, baby formula, pets, washing dishes, water plants, etc. Are the reported screening values protective for all potential routes of exposures (i.e., ingestion, dermal and inhalation)? If not, how can these other routes of exposure be addressed?

5. Please identify any additional scientific issues or questions that the panel should discuss.

Summary Table: MCHM **DRAFT v2.0** **DRAFT v2.0**

	Crude												Pure	
	MSDS for Crude MCHM 1998	Eastman MSDS for Crude MCHM, 2005	Eastman MSDS for Crude MCHM, 2011	Eastman TX-97-306 (1st Oral Tox Rat 14 day)	Eastman TX-99-188 (2nd Acute Oral Tox Rat)	Eastman TX-97-271 (Skin Sensitization)	Eastman TX-97-241 (Ames)	Eastman TX-98-129 (14 day dermal)	Eastman TX-97-308 (Acute dermal tox)	Eastman TX-97-256 (Acute dermal irrit)	Eastman TX-98-004 (Fathead minnow)	Eastman TX-98-005 (Acute daphnid)	The 28-day oral feeding study on pure MCHM (Eastman TX-89-296)	Acute toxicity battery (containing 5 study reports (Eastman TX-90-5)
Ingestion														
Acute oral LD50 (rat)	825 mg/kg	825 mg/kg	825 mg/kg	825 mg/kg	---	---	---	---	---	---	---	---	---	---
Acute oral tox (male rat) LD50	---	---	---	933 mg/kg	---	---	---	---	---	---	---	---	---	---
Acute oral tox (female rat) LD50	---	---	---	707 mg/kg	---	---	---	---	---	---	---	---	---	---
Acute oral LD50 (rat)				---	---	---	---	---	---	---	---	---	---	---
Ingestion	Blood disorders	---	---	---	---	---	---	---	---	---	---	---	---	---
acute oral toxicity in rats testing, LD50 (male)	---	---	---	---	---	---	---	---	---	---	---	---	---	1,768 mg/kg
acute oral toxicity in rats testing, LD50 (female)	---	---	---	---	---	---	---	---	---	---	---	---	---	884 mg/kg
rats for acute oral toxicity,	---	---	---		---	---	---	---	---	---	---	---	---	"slightly toxic by the oral route"
NOEL subacute tox (rat)	---	---	---	---	---	---	---	---	---	---	---	---	100 mg/kg/d	---
Erithropoeitic, kidney, liver tox	---	---	---	---	---	---	---	---	---	---	---	---	400 mg/kg/d minor	---
Dermal					---	---	---	---	---	---	---	---		
Dermal LD50 (rat)	>2000 mg/kg (only dose tested)	>2000 mg/kg (only dose tested)	>2000 mg/kg (only dose tested)	---	---	---	---	NO	>2000 mg/kg (only dose tested), irritant, necrosis	---	---	---	---	---
14-day dermal NOAEL (rat) systemic tox	---	---	---	---	---	---	---	2000 mg/kg		---	---	---	---	---
Repeated dose CHDM (rat 90d)	---	---	8000 mg/L	---	---	---	---				---	---	---	---
Skin irritation (rabbit)	Moderate to strong	strong	strong	---	---	---	---	---	---	Irritating at 0.5 mL of pure	---	---	---	---
Skin sensitization (guinea pig)	None	None	None	---	---	None	---	---	---	---	---	---	---	---
Rats for acute dermal toxicity,	---	---	---		---						---	---	---	"moderately toxic by the dermal route"
Guinea pigs for acute toxicity-dermal irritation,	---	---	---		---	---	---	---	---	---	---	---	---	"a strong skin irritant"
Guinea pigs for acute toxicity – skin sensitization, and	---	---	---		---	---	---	---	---	---	---	---	---	"a strong skin irritant"
Rabbits for acute toxicity-eye irritation.	---	---	---	---	---	---	---	---	---	---	---	---	---	"a moderate eye irritant"
Eyes	Irritation of eyes	---	---	---	---	---	---	---	---	---	---	---	---	---
Serious eye damage;eye irritation (rabbit)	---	---	Moderate	---	---	---	---	---	---	---	---	---	---	---
Dermal	Irritation	---	---	---	---	---	---	---	---	---	---	---		---
Fathead minnow														---
Acute toxicity (fathead minnow, 96 h) - LC50	---	---	57.4 mg/L	---	---	---	---	---	---	---	57.4 mg/L		---	---
Acute toxicity (fathead minnow, 96 h) - NOEC	---	---	25 mg/L	---	---	---	---	---	---	---	25 mg/L		---	---
EU label		---									Harmful to aquatic organisms		---	---
USEPA assessment		---									Moderate concern level		---	---
Daphnid														
Aquatic invertebrates (daphnid, 48 hr) - EC50	---	---	98.1 mg/L	---	---	---	---	---	---	---	---	98.1 mg/L	---	---
Aquatic invertebrates (daphnid, 48 hr) - NOEC	---	---	40 mg/L	---	---	---	---	---	---	---	---	50 mg/L	---	---
Aquatic invert EU label		---		---	---	---	---	---	---	---	---	Harmful to aquatic organisms	---	---
Aquatic invert USEPA assessment		---		---	---	---	---	---	---	---	---	Moderate concern level	---	---
Hematuria														
Hematuria		---	---	Effect	No effect (500 mg/kg)	---	---	---	---	---	---	---	Effect	---
Hematuria - male		---	---	---	---	---	---	---	---	---	---	---	No effect	---
Hematuria - female	---	---	---	---	---	---	---	---	---	---	---	---	Effect. 400 mg/kg, lower mean red blood cell, hemoglobin conc., and hematocrit	---
Blood dissorders	"May cause"													
Liver/Kidney													Effect	
Mutagenicity														
Mutagenicity/Genotoxicity Salmoella-E Coli (Ames)	negative	---	---	---	---		Negative						---	---
Stumbling		---	---	---	Yes (500 mg/kg)		---	---	---	---	---	---		
Inhalation														
Inhalation LC50	Not available	---	---	---	---	---	---	---	---	---	---	---	---	---
Inhalation	Vapor may be irritating	---	---	---	---	---	---	---	---	---	---	---	---	---

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APPENDIX C: SLIDES FROM APRIL 1, 2014 PUBLIC MEETING

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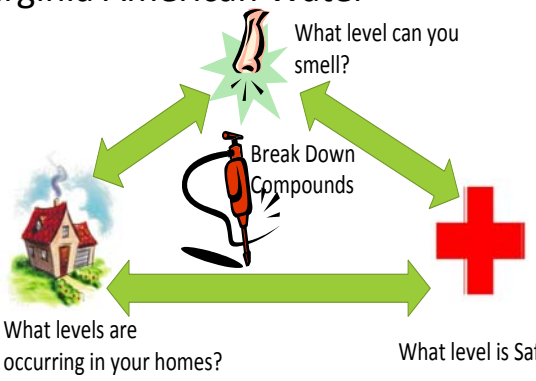
Preliminary Results of the Health Effects Expert Panel

Dr. Michael L. Dourson, Panel Chair
Toxicology Excellence for Risk Assessment (TERA)

April 1, 2014

The WVTAP Program Mission

- Provide independent scientific assessment of the spill of MCHM into the Elk River and its distribution throughout the 9 counties served by West Virginia American Water



Why Convene a Health Effects Expert Panel?

- To provide **independent expert review** of screening levels.
- **Essential part of science**
  - Evaluate by experts who are equivalent (that is "peers") of those who did the work.
  - Review to ensure that results are scientifically sound.
- **Complex issues** require participation by diverse types of scientists.

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Questions to Be Addressed by TAP Expert Panel

- **Review and discuss the available toxicology data** and the scientific support for the West Virginia 4-MCHM Screening Level established at 10 parts per billion (ppb).
- Initial starting value of 1 part per million (1,000 ppb) 4-MCHM established by the CDC and then **consider if the additional safety factor applied by the State of West Virginia was protective of public health**, based on available data.
- **Identify data gaps and make recommendations** for additional studies or analyses that could strengthen the screening level and reduce uncertainty.

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THE Charge Questions

1. Given data now available, what would be appropriate screening levels for MCHM and PPH in drinking water?
2. What additional data, analyses, or studies might reduce uncertainty and provide greater confidence?
3. How should the presence of multiple chemicals in the release to the Elk River be considered?
4. Are the screening values protective for all potential routes of exposures (i.e., ingestion, dermal and inhalation)?
5. Please identify any additional scientific issues or questions that the panel should discuss.

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WV TAP Expert Panel

(affiliations listed for identification purposes only)

- **Dr. Michael Dourson**, Toxicology Excellence for Risk Assessment, Cincinnati, Ohio
- **Dr. Shai Ezra**, Mekorot, Israel National Water Company Ltd, Tel Aviv, Israel
- **Dr. Paul Rumsby**, National Centre for Environmental Toxicology at WRc plc, United Kingdom
- **Dr. Stephen Roberts**, University of Florida, Gainesville, Florida USA
- **Dr. James Jacobus**, Minnesota Department of Health, Saint Paul, Minnesota USA

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Panel's Thoughts on CDC Results

- CDC used traditional methods and reasonable assumptions to develop their screening levels.
- The panel chose to consider additional routes of exposure (inhalation and skin).
- The panel was not constrained to use any particular methods.
- The panel included international and US state experts.

Panel's Approach

- The Panel agreed with CDC on the choice of key toxicity data for MCHM, but not for PPH.
- The Panel agreed with CDC on the choice of uncertainty (safety) factors for MCHM, but had a different choice of factors for PPH.
- The Panel chose to consider additional routes of exposure (inhalation and skin).
- The Panel chose to calculate values based on the most highly exposed population (that is, formula-fed infants).

Exposure & Sensitive Groups

- The Panel considered the following exposures:
  - Direct ingestion of water, including formula-fed infants
  - Inhalation from showering and cooking
  - Skin exposure to water uses in the house
  - Incidental exposures, including brushing teeth, watering plants, etc.
- These exposures protect all populations, including:
  - Infants
  - Children
  - Pregnant Women

Preliminary Conclusions

- The panel developed safe levels of exposure that are protective for all populations.
- These levels are averages for exposures up to 28 days:
  - 120 ppb for MCHM
  - 250 ppb for DiPPH
  - 850 ppb for PPH

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Research Needs

1. Determine MCHM potential to cause skin irritation.
2. Conduct toxicology studies for MCHM in pregnant animals.
3. Organize all available data on exposures and health effects (from immediately following the spill) to facilitate the estimation of initial conditions.
4. Pending results of #2 and #3, consider the need for long term health effects study.
5. Determine chemical fate and transport within the treatment plant and water distribution system.

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The Panel thanks you for the opportunity to help.

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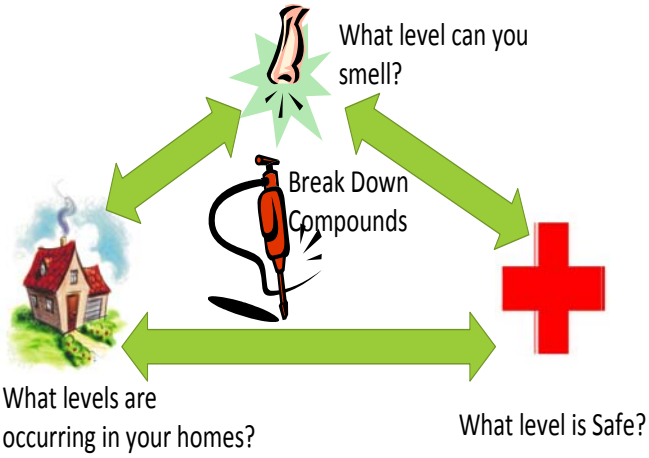
Summary



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Data Postings

- We posted in the last few days
  - Integrated relational database (Access) with all sample results and relevant quality control data
  - Over 1300 pages (12,000 data points) of raw chemical analysis reports
- We will be posting in the next few weeks
  - Odor threshold results for consumer panel
  - Health Effect Expert Panel final report
  - Statistical design for larger sampling program
  - Final report integrating all the results together along with recommendations for next steps and suggested long term research programs.

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Completing the WV Tap Program

- WV TAP anticipated ending in May 15
  - Final report summarizing all the results
  - Includes recommendations to State for short- and long-term activities

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Thank you!

The WV Tap Program

Extra slides

CDC	Panel
No Observed Effect Level (NOEL) = 100 mg/kg-day	No Observed Effect Level (NOEL) = 71 mg/kg-day
Uncertainty Factor = 10H, 10A, 10D	Uncertainty (Safety) Factor = 10H, 10A, 10D (provision for refined factor possible)
Ingestion of water only	Ingestion, inhalation and skin
Exposure to 1-year old child	Exposure to formula-fed infant
Screening level = 1000 ppb	Screening (safe) level = 120 ppb

10H = 10x for human variability; 10A = 10x for animal to human extrapolation; 10D = 10x for data base sufficiency

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CDC	Panel
No Observed Effect Level (NOEL) = 40 mg/kg-day	No Observed Effect Level (NOEL) = 146 mg/kg-day
Uncertainty Factor = 10H, 10A, 10D	Uncertainty (safety) Factor = 10H, 10A, 3D (provision for refined factor possible)
Ingestion of water only	Ingestion, inhalation and skin
Exposure to pregnant woman	Exposure to formula-fed infant (provision for pregnant woman available)
Screening level = 1200 ppb	Screening (safe) level = 850 ppb

10H = 10x for human variability; 10A = 10x for animal to human extrapolation; 10D = 10x for data base sufficiency

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CDC Not Determined	Panel
	No Observed Effect Level (NOEL) = 146 mg/kg-day
	Uncertainty (safety) Factor = 10H, 10A, 10D (provision for refined factor possible)
	Ingestion, inhalation and skin
	Exposure to bottle fed infant (provision for pregnant woman available)
	Screening (safe) level = 250 ppb

10H = 10x for human variability; 10A = 10x for animal to human extrapolation; 10D = 10x for data base sufficiency

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APPENDIX D: WV TAP PRESENTATION SLIDES

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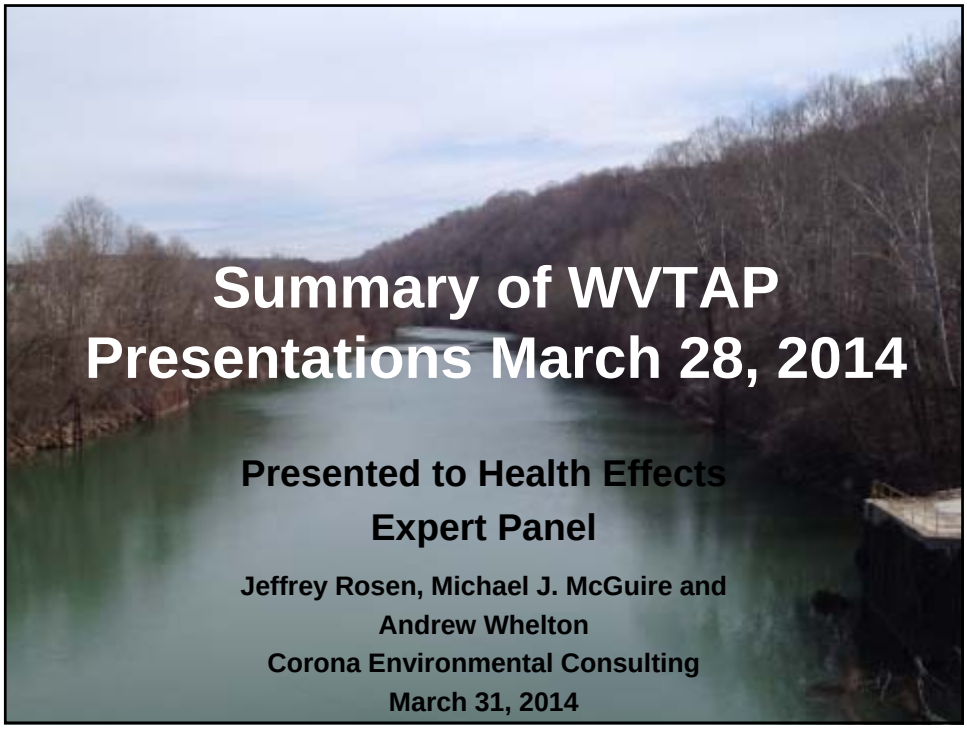
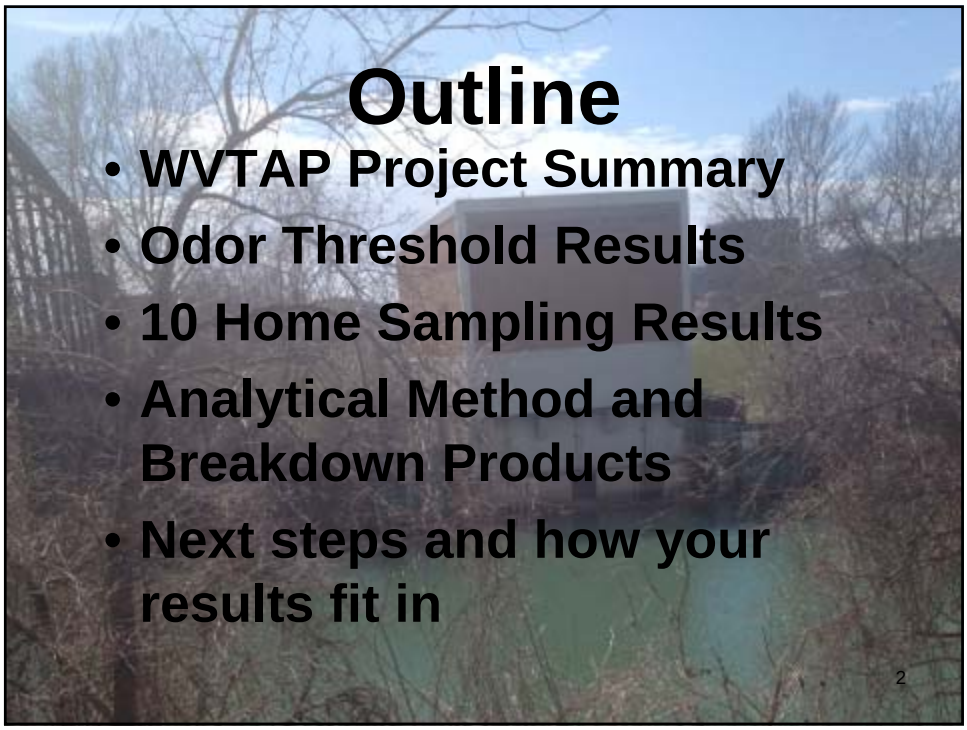


Summary of WVTAP Presentations March 28, 2014

Presented to Health Effects Expert Panel

Jeffrey Rosen, Michael J. McGuire and Andrew Whelton
Corona Environmental Consulting
March 31, 2014



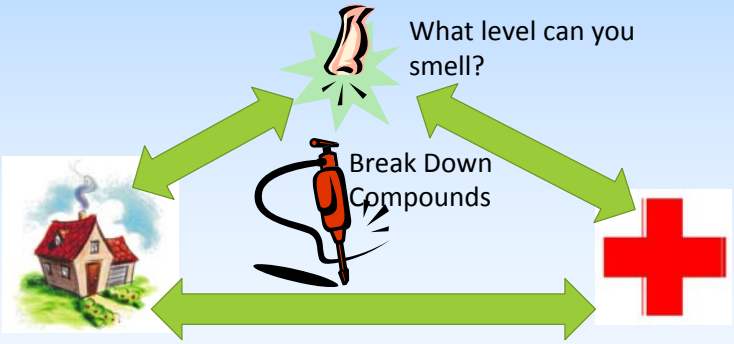
Outline

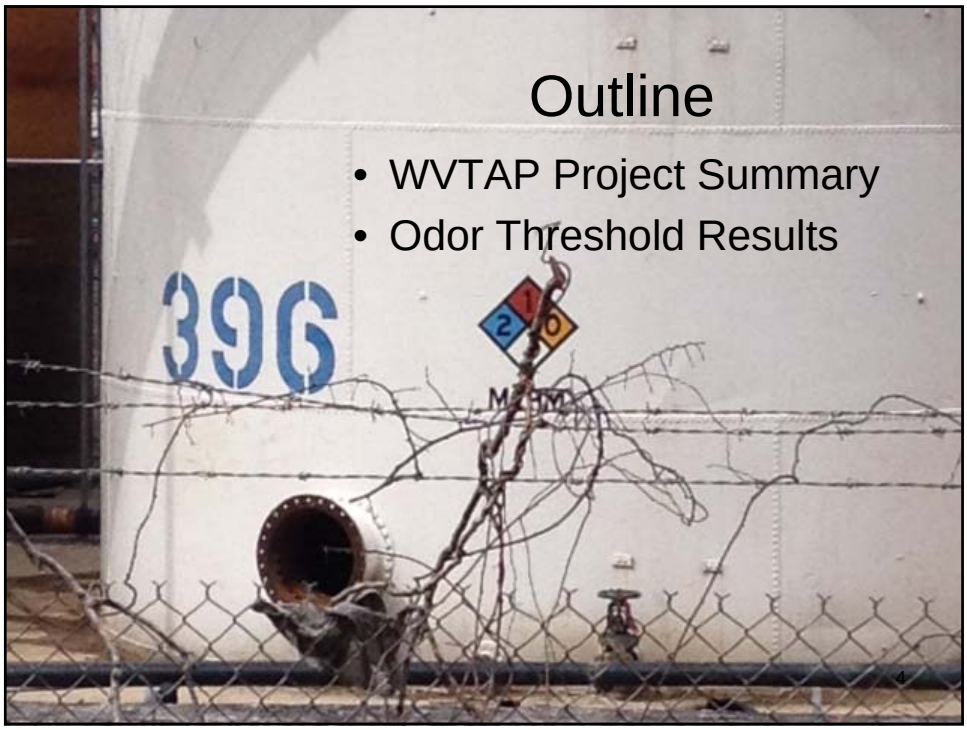
- **WVTAP Project Summary**
- **Odor Threshold Results**
- **10 Home Sampling Results**
- **Analytical Method and Breakdown Products**
- **Next steps and how your results fit in**

2

The WVTAP program mission

- Provide independent scientific assessment of the spill of MCHM into the Elk River and its distribution throughout the 9 counties served by West Virginia American Water





Objectives of Odor Threshold Task

- Develop a method to estimate odor thresholds for the licorice-smelling substance in water
- Convene a panel of odor experts to estimate concentrations of detection, recognition and objection/complaint for the licorice-smelling substance in water
- Understand how the Expert Panel results explain consumer observations in Charleston, WV

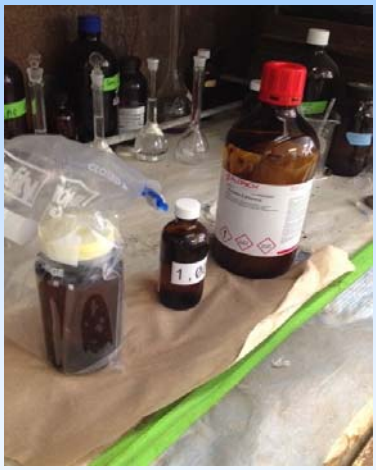
5

Odor Response Terminology

Odor Response	Description	Aesthetic Response Levels
Detection (Threshold)	Chemical concentration usually determined in a laboratory setting where approximately 50% of the panelists can just detect the odor of a chemical	Odor threshold concentration—OTC
Recognition	Concentration of a chemical where a fraction of panelists (defined in the method) can correctly recognize and describe the odor characteristics of the chemical	Odor recognition concentration—ORC
Objection/Complaint	Chemical concentration determined either in a laboratory or field setting that causes consumers to object to their water supply and to call and complain	Odor objection concentration—OOC

Crude MCHM Odor Characteristics

- Crude MCHM has a sharp, irritating licorice odor
- Pure MCHM smells like licorice but is not sharp or irritating
- The odor smelled by consumers in tap water was Crude MCHM
- Crude MCHM spiked into Arrowhead spring water



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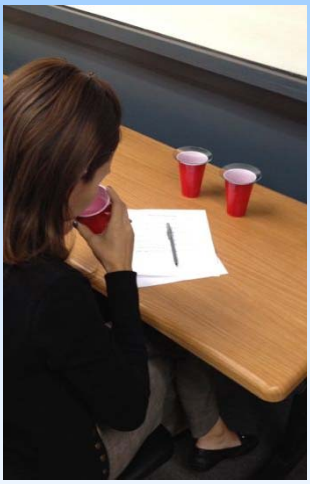
Odor Methodology

- Method ASTM E679-04 (2011)
- 8 concentrations were presented in sets of 3—2 blanks and 1 spiked with Crude MCHM
  - Choose the cup that had a different odor
  - Describe the odor
  - Determine degree of liking
  - Would panelist object/complain about odor?



8

Odor Threshold Findings

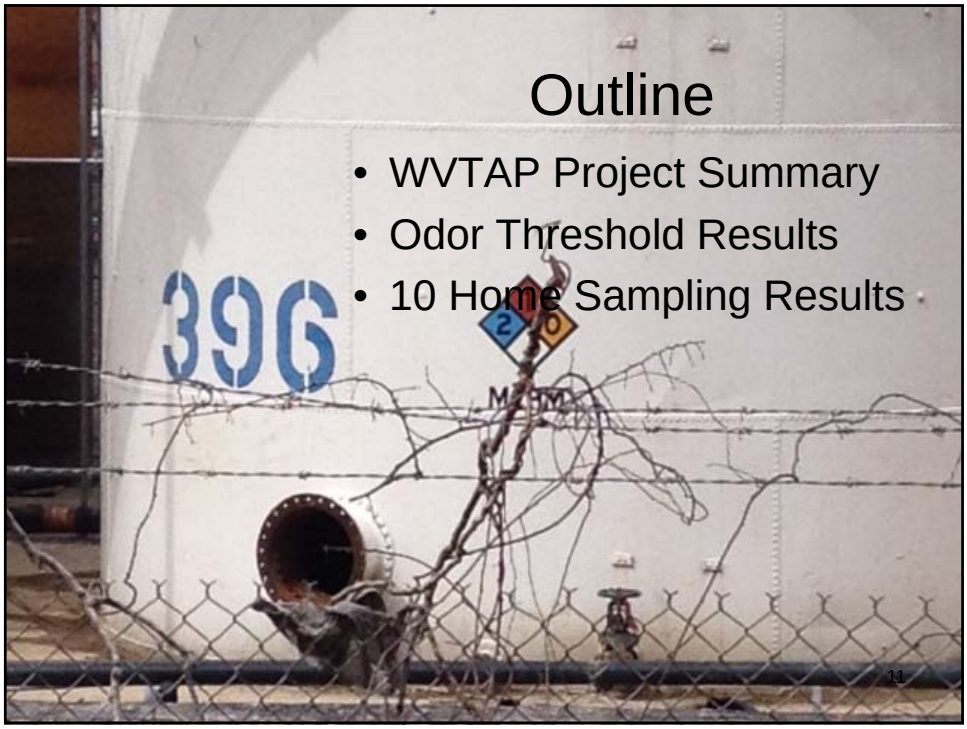
Odor Thresholds	Geometric Mean, ppb	Factor: Greater than OTC
Odor Threshold Concentration (OTC)	less than 0.15	---
Odor Recognition Concentration (ORC)	2.2	15
Odor Objection Concentration (OOC) Based on Degree of Liking	4.0	27
Odor Objection Concentration (OOC) Based on Objection/Complaint	4.0	27

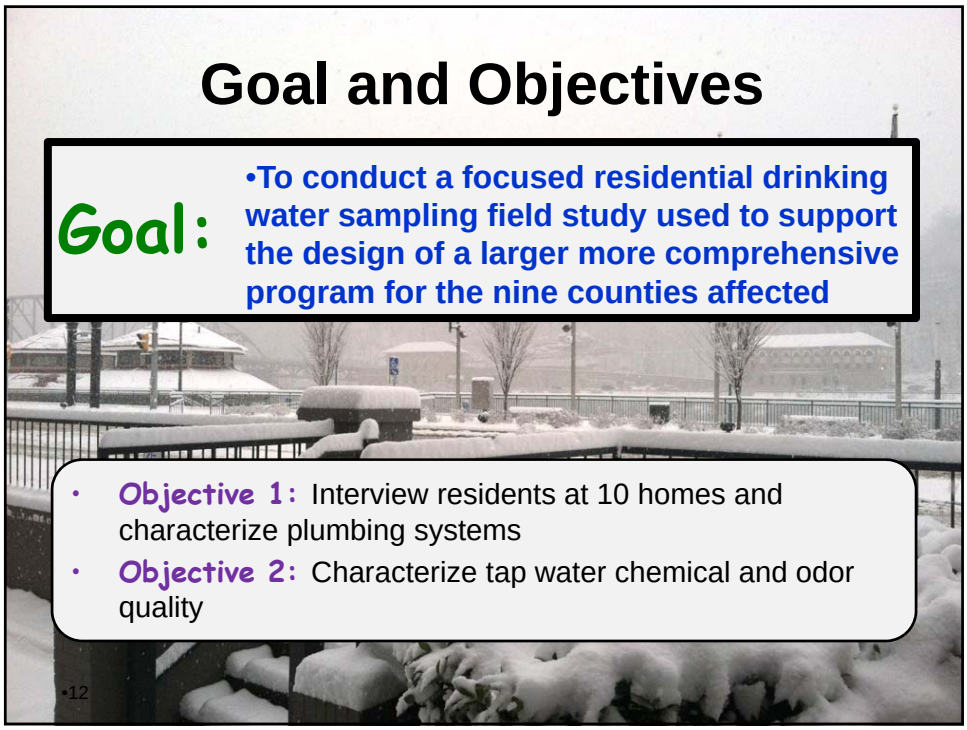
9

Odor Threshold Findings (cont.)

- The estimated thresholds determined in the Expert Panel study support consumer observations in Charleston, WV that people could recognize and object to the licorice odor caused by Crude MCHM in their drinking water even though the analytical reports were showing non-detect at a minimum reporting level of 10 ppb.

10


Outline
• WVTAP Project Summary
• Odor Threshold Results
• 10 Home Sampling Results
396
11

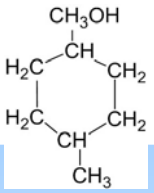

Goal and Objectives
Goal:
•To conduct a focused residential drinking water sampling field study used to support the design of a larger more comprehensive program for the nine counties affected
• Objective 1: Interview residents at 10 homes and characterize plumbing systems
• Objective 2: Characterize tap water chemical and odor quality
•12

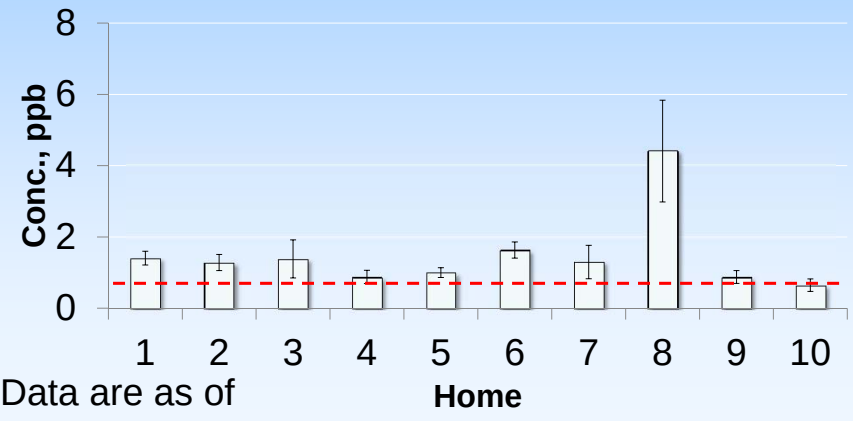
8 of 10 Households Reported Chemical Exposure Symptoms

As of Feb 18, 4 Households Had Sought Medical Assistance

Symptom	No. Households	Ratings
Rash	4	3,4,5,5
Dizziness	4	3,3,3,5
Burning	4	3,3,3,4
Nausea	3	2,3,3
Numbness	2	2,3
Memory loss	2	4,4
Vomiting	1	2
Other: Headache	3	No rating
Other: Flu like symptoms	1	No rating
Other: Agitated	1	No rating
Other: Skin itch	1	No rating
Other: Eyes red	1	No rating

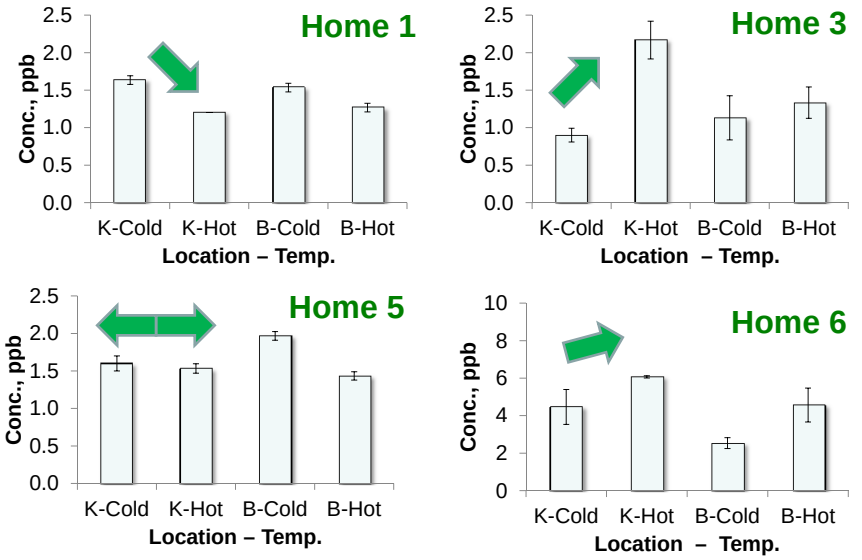
All Home Tap Waters Contained 4-MCHM
No Levels Exceeded 6.1 ppb
90% of the Samples ≤ 2.2 ppb

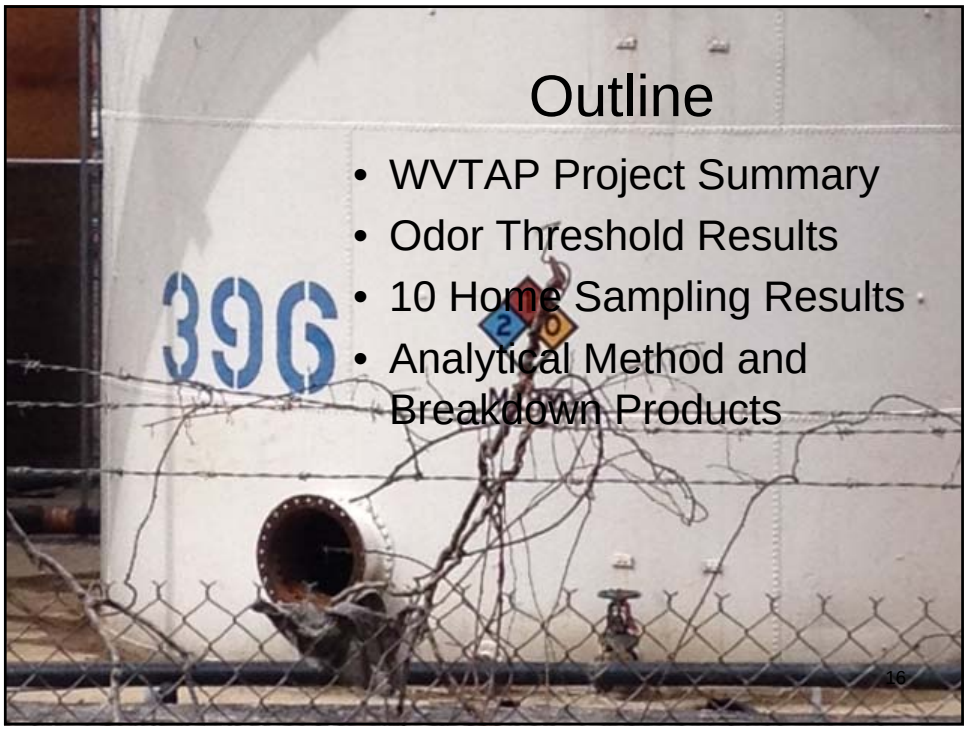




Data are as of February 18, 2014

No Trends were Found between 4-MCHM, In-Home Location, or Water Temperature,
(Data are as of February 18, 2014)





Eurofins 4-MCHM/PPH Analytical Method

Adapted EPA Methods 3510, for the extraction, and 8270D for the analysis. Method 8270D uses GC/MS.

Method 3510 uses methylene chloride to extract (remove) organic compounds from a water sample.

Method Detection Level = 0.5 ppb; Method Reporting Level = 1.0 ppb

These levels are the lowest of any laboratory in the U.S.

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Breakdown Product Findings

- No extraneous compounds found that could not be explained as analytical artifacts (as of 2/18/14)
- No PPH detected in any samples (as of 2/18/14)
- 4-MCHM appears to be the only compound of interest that we are currently detecting in the house samples (about 0.6 ppb) (as of 2/18/14)
- Low levels of 4-MCHM are still coming out of WVAW treatment plant (as of 3/22/2014)
- Focus on GAC as source of low level contamination

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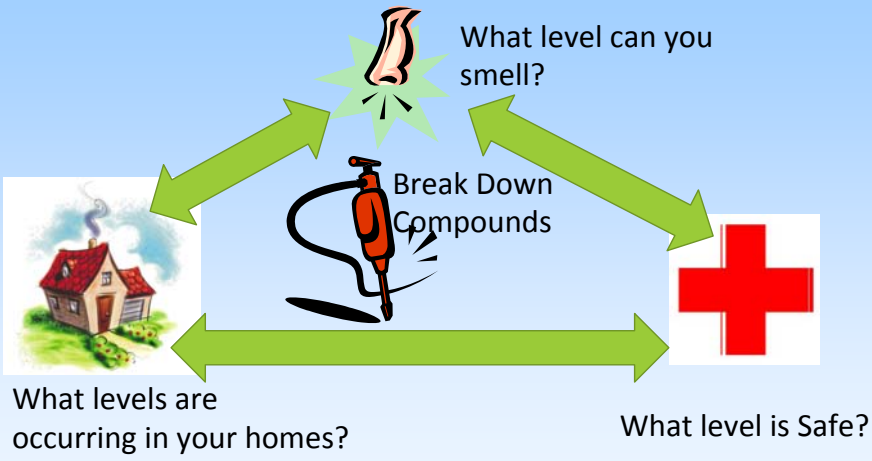
Next Steps

- Access database with all sample results and relevant quality control data has been posted
  - Over 1300 pages (12,000 data points) of raw chemical analysis reports
- Coming weeks
  - Finalization of health effects expert panel report
  - Finalization of report for 10 home study
  - Finalization of report for Consumer odor panel
  - Finalization of design for larger home study
- WV TAP anticipated ending on May 15
  - Final report summarizing all the results
  - Include recommendations to State for short- and long-term activities

The WVTAP program mission



Questions

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APPENDIX E: KANAWHA-CHARLESTON HEALTH DEPARTMENT SYNDROMIC SURVEILLANCE

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Methods Description from Dr. Gupta

Using active syndromic surveillance, we monitored in real-time the frequency of illnesses with a specified set of clinical features not identified with a specific diagnosis. The population for analysis was chosen among patients self-reporting illness symptoms related to MCHM water exposure with onset after January 9, 2014.

Sentinel providers were identified to complete a line list tool. Sentinel providers included physicians and mid-level providers (Nurse Practitioners, Physician Assistants, etc.) who had agreed to report all cases (patients) who presented with self- reported symptoms related to exposure to MCHM. Medical practices were specifically selected based on defined criteria which included: community centered (defined as practices more likely to see those patients presenting with symptoms they reported as related to MCHM exposure as opposed to random specialty practices such as hospitalist, cardiologist etc.); with multiple facility locations in Kanawha and Putnam counties such as large pediatric practices, primary care centers, school-based health centers, and Urgent Cares. The facilities had multiple providers covering a large geographical area and were representative of the two largest counties affected (Kanawha and Putnam).

A line list was developed to collect data on each patient which included:

Demographic data was collected in aggregate and limited to gender and age.

Descriptive epidemiology methods were used to define data collected which including time and place of occurrence (home, work, food facilities, other) and the self-reported symptoms of the persons affected.

The list included multisystem symptoms (respiratory, digestive, integumentary (skin), neurological)

Respiratory: cough, sore throat

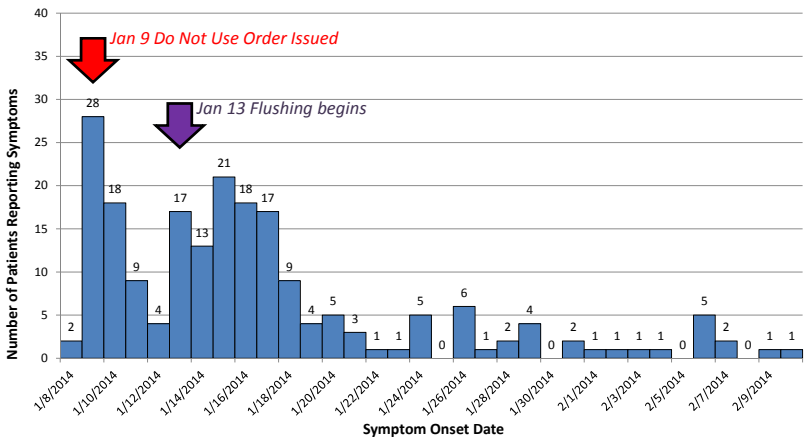
Digestive: nausea, vomiting, diarrhea

Skin: rash, skin irritation

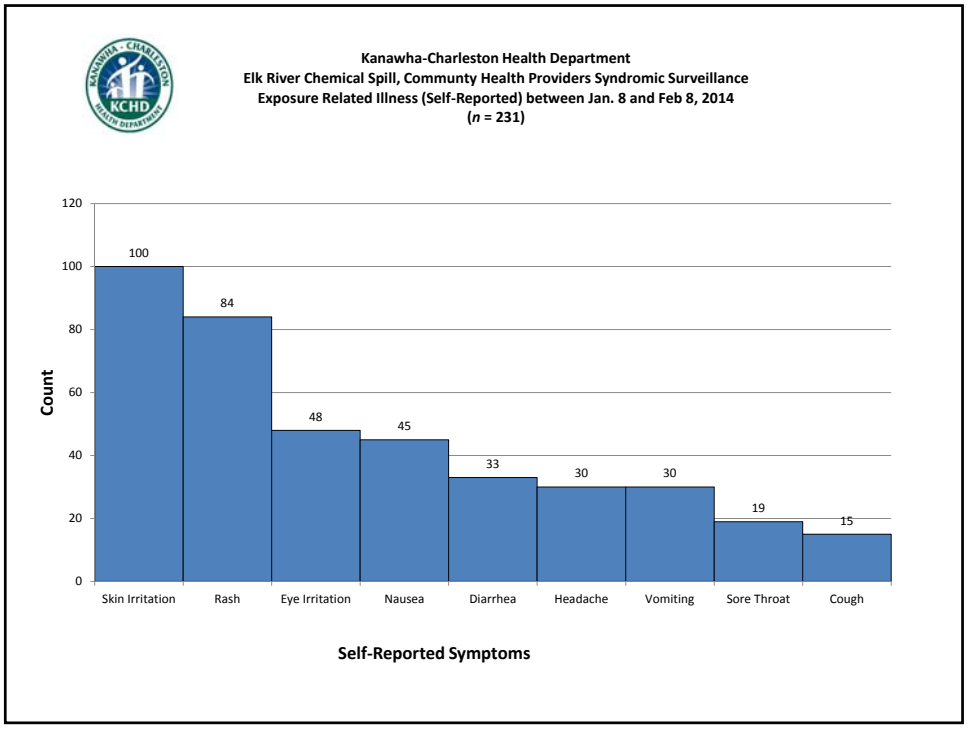
Neurological: Headache

As symptoms had not been defined we included a column: Other symptoms

Kanawha-Charleston Health Department
Elk River Chemical Spill, Community Health Providers Syndromic Surveillance



Data represent only 10 multi-provider practices; There are at least 1,300 providers in the area


Kanawha-Charleston Health Department
Elk River Chemical Spill, Community Health Providers Syndromic Surveillance
Exposure Related Illness (Self-Reported) between Jan. 8 and Feb 8, 2014
(n = 231)
Count
120
100
80
60
40
20
0
100
84
48
45
33
30
30
19
15
Skin Irritation
Rash
Eye Irritation
Nausea
Diarrhea
Headache
Vomiting
Sore Throat
Cough
Self-Reported Symptoms