TERA
TOXICOLOGY EXCELLENCE FOR RISK ASSESSMENT

Short Term Health Advisories for Elk River Spill

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National Academy of Sciences
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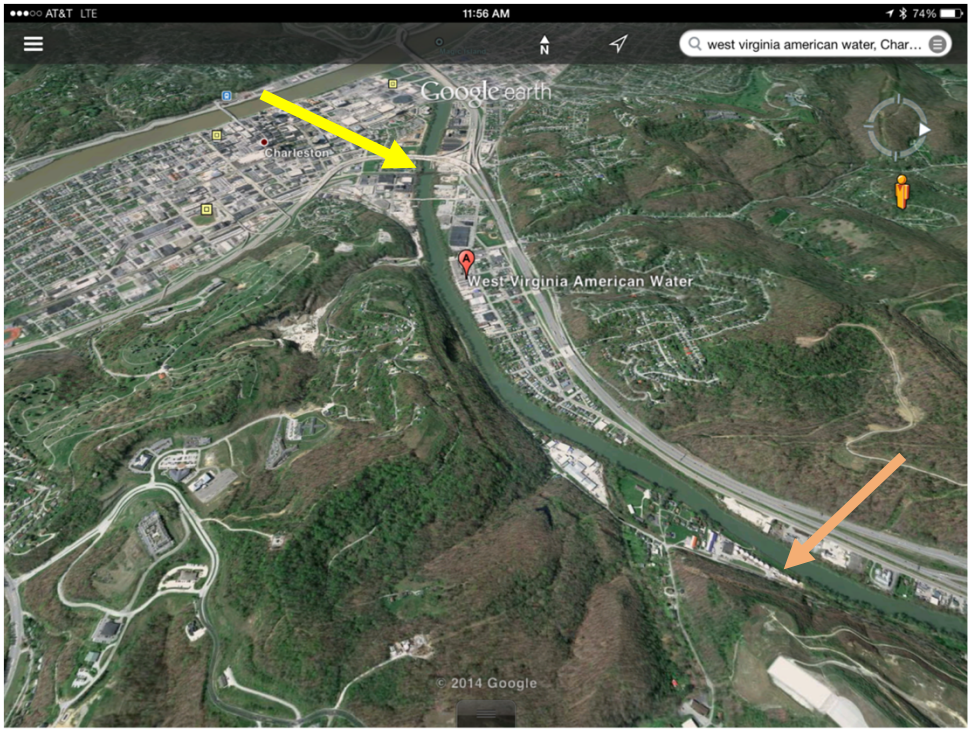
Talk Outline:
Introduction
What level is Safe?
Ongoing Research
West Virginia

Freedom Industries, Inc.

Spill occurred from tank 396 and later discovered also from 397

Introduction: Window of Detection and Action



- About 1 mile from intake.
- Travel time estimated to be 1.1 – 1.8 hours
- Spill may have started a few days before it was detected.
- First detection, human olfactory sensors.
- Freedom Inc. knew about the spill and was trying to clean it up when it was discovered by state DEP

What Was Spilled?

- **Crude MCHM (Eastman) 88.5%**
  - Used in coal processing
  - The Crude MCHM is a mixture containing:
    - **4-Methyl-1-cyclohexanemethanol (MCHM) @ 68-89% (w/w);**
    - 4-(Methoxymethyl) cyclohexane methanol (**MMCHM**) @ 4-22% (w/w) ;
    - Methyl 4-methylcyclohexane-1-carboxylate (**MMCHC**) @ 5% (w/w);
    - 1,4-Dimethyl cyclohexanedicarbonate (**DMCHDC**) @ 1-2% (w/w);
    - 1,4-Cyclohexanedimethanol (**CHDM**); and
    - Methanol (**MeOH**) @ 1-2% (w/w).
- **DOW PPH Basic 7.3%**
  - It is reported that the source of the Freedom Industries' PPH was DOW PPH Basic
  - DOW Basic contains:
    - Dipropylene glycol phenyl ether (**DiPPH**) concentration at between 40% and 85%;
    - Propylene glycol phenyl ether (**PPH**); and
    - Other compounds.

CDC Advisory MCHM

- January 9, 2014, January 20, 2014
- Methodology: EPA DW advisory methods (Donohue and Lipscomb, 2002)

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

- NOEL: 100 mg/kg-day (Eastman, 1990)
- Consumption:
  - BW of a child: 10 kg
  - Intake: 1 liter/day, water intake for child.
- Uncertainty Factors (UF): 1000 (UFA, UFH, UFDB)
- **1 ppm or 1000 ppb screening level**

CDC (2014) "Information about MCHM - 2014 West Virginia Chemical Release" http://www.bt.cdc.gov/chemical/MCHM/westvirginia2014/mchm.asp . January 20

WV TAP Expert Panel

(affiliations listed for identification purposes only)

Expertise in toxicology, risk assessment, deriving risk values for water contaminants, and water quality and distribution systems.

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

What Level is Safe?

TASK: Independently evaluate the safe levels of MCHM and PPH for all members of the population for all intended uses

- Comprehensive literature review of relevant toxicological literature (Adams, 2014)
- Health Effects Expert Panel on March 31, 2014 in Charleston, West Virginia: evaluate available toxicity data and health advisories

Specific Charge Questions to Panel

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. Other issues?

Available Data on MCHM – very limited

- Crude MCHM, acute gavage in rats, 250 - 1000 mg/kg-day; Possible hematuria (Eastman 1998, 1999)
- Pure MCHM, gavage in rats Eastman (1990)
  - 0, 25, 100, and 400 mg/kg/day, 5 days a week, for 4 weeks
  - 400 mg/kg/day – anemia (F), kidney and liver effects
  - NOEL 100 mg/kg/day
  - Proprietary, OECD and GLP
  - **Study used by CDC**

Critical Effect of MCHM?

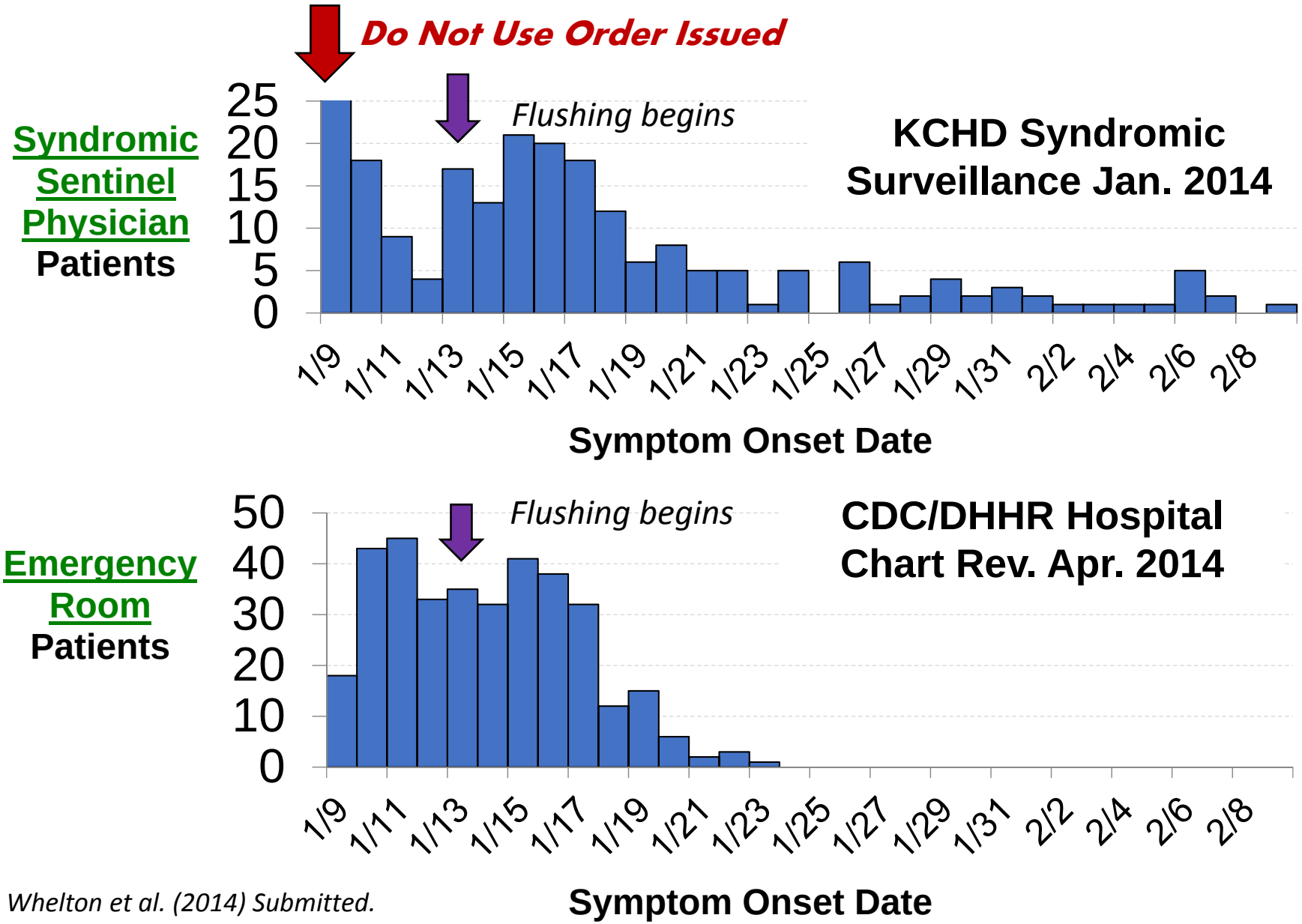
Absolute kidney weights for male rats heavier at 25 mg/kg.
Relative kidney weights statistically heavier for all treated males.

No differences were seen in female rats.

Relative and absolute changes might be adverse. However:

- 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
- Low dose effects did not have matching clinical changes or histopathology, which when compared with organ weight changes, are more definitive.

Plumbing System Flushing: REAL-TIME Syndromic Surveillance Would Have Revealed Illnesses were being Caused



Whelton et al. (2014) Submitted.

WV TAP Expert Panel

- CDC used traditional methods and reasonable assumptions to develop their screening levels

- The Panel considered additional exposure routes:
  - 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.

- The Panel determined formula-fed infants to be the most highly exposed population/life stage

Panel Advisory for MCHM

- Methodology – not constrained, used full experience
- NOEL: 100 mg/kg-day (Eastman, 1990)
  - Adjusted to 71 mkd for 5 day/week dosing
- Consumption: 0.285 liters/kg bw (95th percentile)
  - Formula fed infant - most exposed life stage
- Allow for other possible sources and routes of exposure (i.e., dermal, inhalation): factor of 0.5
- Uncertainty Factors (UF): 1000 (UFA, UFH, UFDB)

Panel Calculated Level for MCHM

DW Advisory Level = (NOEL × BW) / (UF × Intake)

→ DW Advisory Level ≤ [(NOEL) / (UF × Intake/BW)] · Exposure factor

where:

DW Advisory Level is the drinking water advisory level (µg/L or ppb)

NOEL = No Observed Effect Level in the experiment = 71 mg/kg/day

UF = uncertainty factors (unitless)

- for differences between humans and animals (10x)
- to account for more sensitive humans (10x)
- to account for in the toxicity database data (10x)

Intake / BW = water consumed daily by a bottle-infant (0.285 L/kg·d)

Exposure factor = to account for other sources of exposure (0.5)

4-week DW Advisory Level = (NOEL) / (UF × Intake/BW) · Exposure factor

= [(72 mg/kg/d)] / [(10×10×10) = 0.0072 (rounded to 0.07)

0.07 mg/kg-day / (0.285 L/kg·day)] · 0.5 = 0.123 mg/L (rounded to 120 µg/L)

What about the Mixture?

- Toxicity data on specific chemical mixtures are rarely available.
- Toxicity of mixtures in spill could be approximated by a simple additive approach (MCHM, PPH, DiPPH, etc) following US EPA's mixtures guidelines (US EPA 1986 and 2000)
- For example, it is reasonable to assume that the toxicity of the mixture (Crude MCHM) would be similar to the pure MCHM.

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.

US NTP Study Summary

Test Article [Abbreviation, CAS Number]	Studies							
	Rat Prenatal Toxicity	Mouse Dermal Irritation and Hypersensitivity	5-Day Rat Toxicogenomic	Bacterial Mutagenicity	Zebrafish Developmental	Nematode Toxicity	High Throughput Screening	Structure Activity Relationship (SAR) Analysis
4-Methylcyclohexanemethanol [MCHM, 34885-03-5]	A	A	A	X	X	X	X	A
Dipropylene glycol phenyl ether [DiPPH, 51730-94-0]				X	O	X		X
Propylene glycol phenyl ether [PPH, 770-35-4]			A	X	X	X	X	X
1,4-Cyclohexanedimethanol (CHDM, 105-08-8)				O	X	X	X	A
2-Methylcyclohexanemethanol [2MCHM, 2105-40-0]				X	O	*		A
4-(Methoxymethyl)cyclohexanemethanol [MMCHM, 98955-27-2]				X	O	X		A
Dimethyl 1,4-cyclohexanedicarboxylate [DMCHDC, 94-60-0]				O	A	X	X	A
Methyl 4-methylcyclohexanecarboxylate [MMCHC, 51181-40-9]				X	O	*		A
Technical product ["crude MCHM"]		A	A	X	X	X		
Commercial Product (Dowanol DiPPh glycol ether)				X		X		
Cyclohexanemethanol, 4-((ethenyloxy)methyl)- [114651-37-5]					O	X	X	A
4-Methylcyclohexanecarboxylic acid [4331-54-8]					O	X		A
Cyclohexanemethanol, alpha,alpha,4-trimethyl- [498-81-7]					X	X	X	A
Phenoxyisopropanol [4169-04-4]					X	X	X	X

X= done and are inactive/negative; A= done and are active/positive; O = data will be available by early to mid June

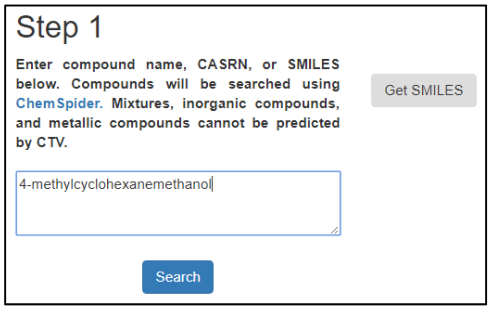
*Were not available at the time of testing, are currently available, and may still be tested; structural analogs are shown in yellow (not found in the spilled material)

US NTP Summary of Findings

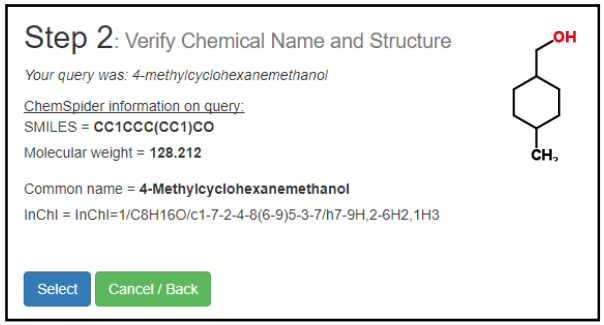
- SAR indicated that the MCHM class of chemicals may be irritating to the skin and sensory organs, and toxic to developing animals.
- None of the chemicals from the spill that were tested in HTS and Nematode Toxicity Studies were active.
- None of the chemicals from the spill except DMCHDC (very minor spill component) that were tested in the Zebrafish Developmental Toxicity Studies were active.
- None of the chemicals from the spill that were tested in Bacterial Mutagenesis and In vivo Micronucleus Studies were positive.
- MCHM and crude MCHM produced changes in biological activity at doses of approximately 100 mg/kg/day (approximates 1000 ppm in drinking water). PPH produced changes in biological activity at doses in the range of 1 mg/kg/day (approximates 30 ppm in drinking water).
- MCHM was a mild irritant but not a sensitizer and crude MCHM was a mild irritant and weak sensitizer.
- At doses well in excess of the drinking water advisory level MCHM was toxic to developing rats. Toxicity in the developing rats was observed at dose levels where there was no maternal toxicity. The most sensitive effect in the Rat Developmental Toxicity Study of MCHM was decreased fetal weight.

Toxvalue.org: Online Portal for QSAR Predictions

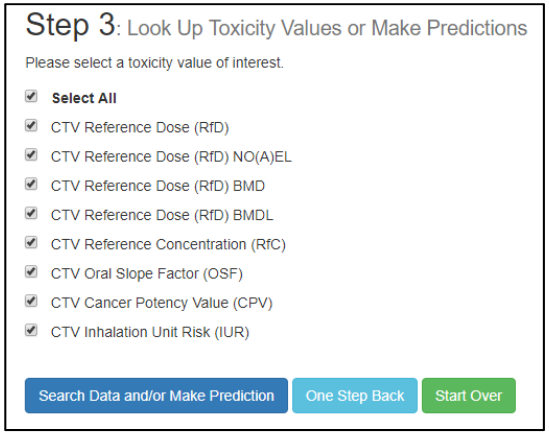
Search for a chemical (3-10 seconds)



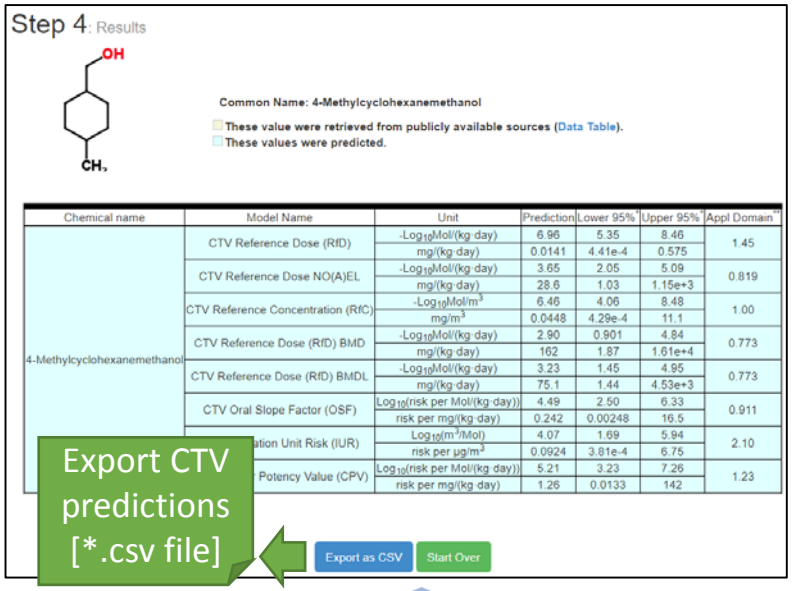
Verify chemical's identity



Select Toxicity Value(s) of interest



Run CTV QSAR models (~30 seconds)



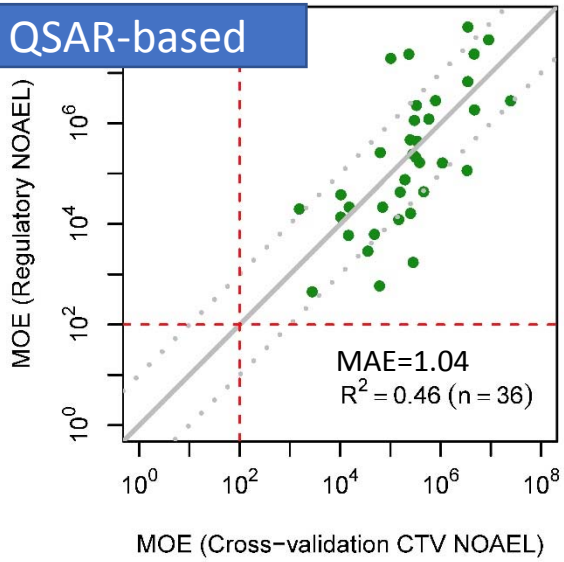
Chemical name	Model Name	Unit	Prediction	Lower 95%	Upper 95%	Appl Domain
4-Methylcyclohexanemethanol	CTV Reference Dose (RfD)	-Log10Mol/(kg·day)	6.96	5.35	8.46	1.45
		mg/(kg·day)	0.0141	4.41e-4	0.575	
	CTV Reference Dose NO(A)EL	-Log10Mol/(kg·day)	3.65	2.05	5.09	0.819
		mg/(kg·day)	28.6	1.03	1.15e+3	
	CTV Reference Concentration (RfC)	-Log10Mol/m3	6.46	4.06	8.48	1.00
		mg/m3	0.0448	4.29e-4	11.1	
	CTV Reference Dose (RfD) BMD	-Log10Mol/(kg·day)	2.90	0.901	4.84	0.773
		mg/(kg·day)	162	1.87	1.61e+4	
	CTV Reference Dose (RfD) BMDL	-Log10Mol/(kg·day)	3.23	1.45	4.95	0.773
		mg/(kg·day)	75.1	1.44	4.53e+3	
	CTV Oral Slope Factor (OSF)	Log10(risk per Mol/(kg·day))	4.49	2.50	6.33	0.911
		risk per mg/(kg·day)	0.242	0.00248	16.5	
	ation Unit Risk (IUR)	Log10(m3/Mol)	4.07	1.69	5.94	2.10
		risk per µg/m3	0.0924	3.81e-4	6.75	
	Potency Value (CPV)	Log10(risk per Mol/(kg·day))	5.21	3.23	7.26	1.23
		risk per mg/(kg·day)	1.26	0.0133	142	

Export CTV predictions [*.csv file]

Better (more accurate/precise) than using in vitro data?

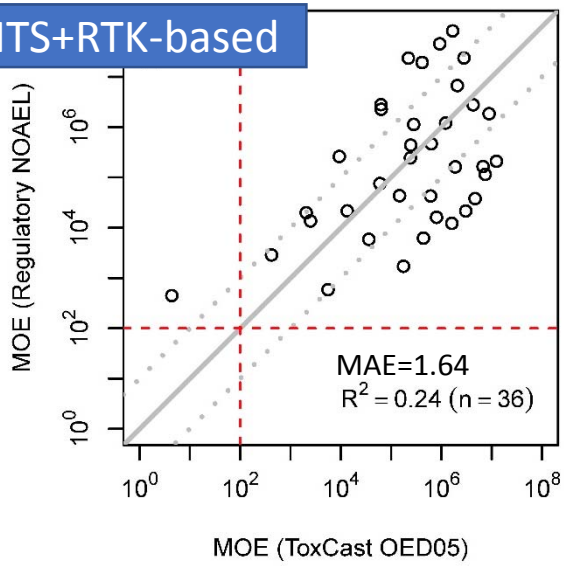
- Large-scale efforts in Federal government to develop toxicity values for screening and prioritization based on
  - In vitro high throughput screen (HTS) assays
  - Reverse toxicokinetics (RTK) to convert in vitro concentrations to oral equivalent doses
- Can evaluate performance relative to "gold standard" of regulatory toxicity values.
- MOE and HI using QSAR-based toxicity values are **more accurate and precise** than those based on HTS+RTK data

QSAR-based



QSAR-based values have larger R^2 and smaller MAE

HTS+RTK-based



Example: West Virginia Elk River 4-Methylcyclohexanemethanol spill

No regulatory toxicity value!

"Rapid" generation of toxicity values

- ***Days after spill:***
  CDC screening level corresponding to 0.1 mg/kg-d
- ***Months after spill:***
  Toxicology consultants derived short term RfD of 0.07 mg/kg-d (TERA panel value)

<u>If CTV were available at the time:</u>

- ***Minutes after the spill:***
  Chronic RfD of 0.014 mg/kg-d (90% CI: 0.0004 to 0.58) (~1500-fold)

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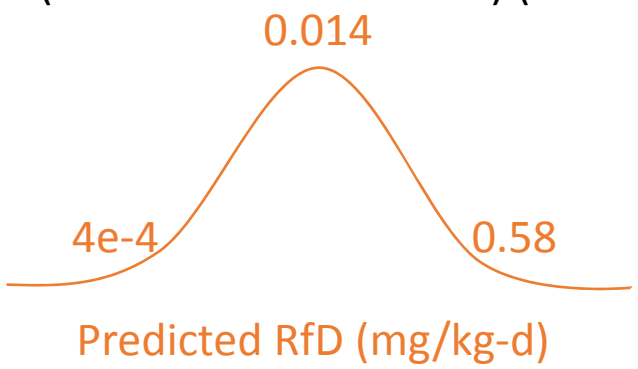

Summary

- The WV TAP Expert Panel reviewed the CDC and WV screening values and reached conclusions that are not incompatible with the CDC values. NTP and other research is also consistent.

- Panel used more refined methods than CDC, including an adjustment to account for dermal and inhalation exposure.

- Newer research extends the work of both CDC and TERA Panel.

- MCHM concentrations below 120 ppb are safe for ALL members of the community for ALL intended uses for up to 1 month of exposure. A lifetime health advisory may be lower.

Acknowledgements

- WV TAP Technical Team
  - Jeffrey Rosen, Program Manager
  - Andrew Whelton, University of South Alabama
  - Craig Adams, Utah State University

- Funding and support from:
  - West Virginia Bureau for Public Health (WVBPH)
  - West Virginia Department of Health and Human Resources (WVDHHR).

More Information and References

Expert Panel Report

- http://www.tera.org/Peer/WV/WV%20Expert%20Report%2012%20May%202014.pdf

WVTAP Web Site

- http://www.dhsem.wv.gov/wvtap/test-results/Pages/default.aspx

Questions?

<<< >>>

Extra Slides

WVTAP Literature Review

Adams, C., Whelton, A., Rosen, J. (2014) "Health Effects for Chemicals in 2014 West Virginia Chemical Release: Crude MCHM Compounds, PPH and DiPPH,"

Public report by West Virginia Testing Assessment Project (WV TAP) to the State of West Virginia.

Very limited data for MCHM

Additional Question by WV for the Expert Panel

- **Was the additional safety factor applied by the State of West Virginia protective of public health, based on available data?**

  - CDC initial screening value of 1 ppm (1,000 ppb) 4-MCHM
  - WV screening level later set at 10 ppb

Was the additional safety factor applied by the State of West Virginia was protective of public health, based on available data?

--CDC initial screening value of 1 ppm **(1,000 ppb)**
--WV screening level later set at **10 ppb**

- Panel derived short-term advisory of **120 ppb**
- Protect all portions of the population (inc. infants, children, pregnant women)
- Protect for exposures from direct ingestion, inhalation from showering and household water use, dermal exposure.
- Appropriate for apply to exposure situations of 1 day up to 3 months.

What Was Spilled?

- **Crude MCHM (Eastman) 88.5%**
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  - The Crude MCHM is a mixture containing:
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    - 1,4-Cyclohexanedimethanol (**CHDM**); and
    - Methanol (**MeOH**) @ 1-2% (w/w).
- **DOW PPH Basic 7.3%**
  - It is reported that the source of the Freedom Industries' PPH was DOW PPH Basic
  - DOW Basic contains:
    - Dipropylene glycol phenyl ether (**DiPPH**) concentration at between 40% and 85%;
    - Propylene glycol phenyl ether (**PPH**); and
    - Other compounds.

Key Studies for PPH

- Oral toxicological data on PPH include:
  - A 90-day drinking water study (and 28-day range finding study) in rats (OECD 408 – BASF AG 1997a) study used by PANEL
  - A two-generation study drinking water study in rats (OECD 416 – BASF 2000)
  - A prenatal developmental toxicity studies using gavage with rats (OECD 414 – BASF AG 2000) and rabbits (OECD 414 – BASF AG 1995 and OECD 2006c) study used by CDC
  - In vitro and in vivo genetic toxicity tests

WV TAP Panel Screening Level for PPH

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

→ DW Advisory Level ≤ [(NOEL) / (UF × Intake/BW)] · Exposure factor

where:

DW Advisory Level is the drinking water advisory level (µg/L or ppb)

NOEL = No Observed Effect Level in the experimental species = 146 mg/kg/day (from 90-day DW study)

UF = uncertainty factors (unitless)

for differences between humans and animals (10x)

to account for more sensitive humans (10x)

to account for in the toxicity database data (3x)

Intake / BW = water consumed daily by a bottle-infant (0.285 L/kg·d)

Exposure factor = factor to account for other sources of exposure other than ingestion (i.e., inhalation, dermal) (0.5)

90-day DW Advisory Level = (NOEL) / (UF × Intake/BW) · Exposure factor

= [(146 mg/kg/d)] / [(10×10×3) = 0.49 (rounded to 0.5 for a short term RfD)

0.5 mg/kg-day / (0.285 L/kg·day)] · 0.5 = 877 (rounded to 880 µg/L or ppb)

Comparison CDC to Panel for PPH

CDC	TERA PANEL
No Observed Adverse Effect Level (NOAEL) = 40 mg/kg-day teratology study in rats, maternal toxicity	NOAEL = 146 mg/kg-day ((ECHA, 2014), 90-day DW study in rats
Uncertainty Factor = 10H, 10A, 10D	Uncertainty Factor = 10H, 10A, 3D (missing second repeat dose tox study)
Intake = 1 liter water/day (child) Body Weight = 10 kg (child)	0.285 liters/kg bw (95th percentile) Formula fed infant most exposed life stage
Ingestion of water only	RSC = 0.5 to allow for other possible sources and routes of exposure (i.e., dermal, inhalation)
PPH Screening Level = 1200 ppb	PPH Short-Term Health Advisory = 880 ppb

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

WV TAP Panel Screening Level for DiPPH

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

→ DW Advisory Level ≤ [(NOEL) / (UF × Intake/BW)] · Exposure factor

where:

DW Advisory Level is the drinking water advisory level (µg/L or ppb)

NOEL = No Observed Effect Level in the experimental species = 146 mg/kg/day (from 90-day DW study)

UF = uncertainty factors (unitless)

for differences between humans and animals (10x)

to account for more sensitive humans (10x)

to account for in the toxicity database data (10x)

Intake / BW = water consumed daily by a bottle-infant (0.285 L/kg·d)

Exposure factor = factor to account for other sources of exposure other than ingestion (i.e., inhalation, dermal) (0.5)

90-day DW Advisory Level = (NOEL) / (UF × Intake/BW) · Exposure factor

= [(146 mg/kg/d)] / [(10×10×10) × (0.285 L/kg·d)] · 0.5 ≤ 256 or 260 µg/L (ppb)

Note short term Reference Dose not calculated since toxicity is based on PPH.

PPH and DiPPH

- CDC
  - PPH: 1200 ppb
  - DiPPH: Limited data suggest similar or lower toxicity, the PPH screening value would also be protective for DiPPH.
- Expert Panel
  - PPH: 880 ppb
  - DiPPH:260 ppb

  See expert panel report for details - http://www.tera.org/Peer/WV/WV%20Expert%20Report%2012%20May%202014.pdf