Denka
Denka Performance Elastomer

Request to Correct IRIS' 2010 Toxicological Review of Chloroprene

June 28, 2017

DPE Presentation Agenda

- Introductions – Nao Kawamura, Vice President of Administration
- Overview of Denka Performance Elastomer– President and CEO Koki Tabuchi
- Summary of basis for requesting correction– Plant Safety, Health, and Environmental Manager Patrick Walsh, CIH

Overview of Denka Performance Elastomer

Denka Performance Elastomer LLC

- Formed to purchase Neoprene business from DuPont
- American entity with two parent companies from Japan
  - Denka Denka Company Limited - 70% Ownership
    - Leading Chemical Co in Japan
    - 100 year history
    - Elastomers, Performance Plastics, Inorganic Materials, Electronics, Life Science
    - 6 Domestic Plants, 9 Overseas including Pontchartrain
  - Mitsui & Co. – 30% Ownership

- Always strive for excellence in safety and environmental stewardship
- Will work to maintain place as integral member of the community and a good neighbor

SITE DEMOGRAPHICS & STATISTICS

	NEOPRENE
TOTAL EMPLOYEES	*249*
RIVER PARISH RESIDENTS	*77%*
AVERAGE SERVICE YEARS	*19*
ANNUAL PAYROLL	*$33MM*
RES. CONTRACTORS	*125*
APPROXIMATE PAYROLL	*$8.1MM*
TAXES (STATE & LOCAL)	*$1.9MM*
VALUE OF PURCHASES	*$76.5MM*

Third largest private employer in St. John Parish

DPE to URE

- 11/1/15: DPE takes ownership of the only Neoprene plant in North America after purchase from DuPont
- 12/17/15: EPA released National Air Toxics Assessment– study states that emissions from plant cause highest off -site cancer risk for any source in the country
- The NATA risk calculations are based on facility emissions andon an erroneous and ultrahigh Unit Risk Estimate from IRIS' 2010 Review
- The 2010 IRIS Toxicological Review of Chloroprene established an overly stringent inhalation Unit Risk Estimate (URE) or Inhalation Unit Risk (IUR) of **5×10^{-4} /µg/m^3** for a 70-year, lifetime exposure.
- URE has been applied to calculate a 100-in-a-million cancer risk with annual average chloroprene concentrations of **0.2 µg/m^3**

Summary of DPE's Request for Correction

Request for Correction – Summary of Bases

- Brings study in line with recommendations from NAS/NRC
- Toxicological evidence
- Epidemiological evidence
- IUR derivation corrections
- PBPK modeling results

NAS/NRC Recommendations

- NRC has issued guidance on IRIS process in 2011 and 2014
  - Better transparency and rigor—some portions of 2010 Review cannot be reconstructed
  - Better evaluation of weight-of-evidence—certain weaker studies in 2010 Review given higher priority
- Congress directed, and EPA agreed, to adopt the NRC recommendations
- 2010 Review published before these guidelines issued—updating the Review would bring the study in line with those recommendations

Toxicological Evidence – 1

- Too much weight was given to the most sensitive species with inconsistent results across species
  - Study identified unique sensitivity in female mice – this became a cornerstone of the IRIS Review
  - Did not attempt to account for important pharmacokinetic differences between mice and humans

Toxicological Evidence – 2

- Mode-of-action (MOA) in 2010 Review needs to be updated
  - 2010 Review hypothesizes a mutagenic MOA due to structural similarities with vinyl chloride and 1,3-butadiene
  - Published data does not support this—even NTP study states that chloroprene was not mutagenic in any of their tests

Epidemiological Evidence – 1

- Too much weight applied to poor quality epidemiological studies, and not enough to the most high quality study
  - Most robust study (Marsh, et al. 2007) treated the same as less rigorous Russian, Armenian, and Chinese studies
  - Marsh study concluded that there is no link between occupational exposure to chloroprene and cancer mortality of any type
  - 2010 Review disregarded Marsh study conclusion and focused on statistically insignificant increase in liver cancers observed in three subgroups because comparison group exhibited fewer cancers than expected

Epidemiological Evidence – 2

Rank	County	Annual Incidence Rate(†) over rate period - cases per 100,000	Average Annual Count over rate period	Rate Period	Recent Trend	Recent 5-Year Trend (‡) in Incidence Rates
53	St. John the Baptist Parish(7,9)	460.8	209	2008-2012	stable	-2.2

IARC(*), 1999: "There is inadequate evidence in humans for the carcinogenicity of chloroprene."

*International Agency for Research on Cancer

http://statecancerprofiles.cancer.gov/incidencerates/index.php?stateFIPS=22&cancer=001&race=00&sex=0&age=001&type=incd&sortVariableName=rate&sortOrder=default#results

https://monographs.iarc.fr/ENG/Monographs/vol71/mono71 -9.pdf

Overly Conservative Derivation of IUR

- 2010 Review interpreted the animal studies incorrectly
  - Treated each tumor as unique event, causing animals with multiple tumors to be counted twice in the risk analysis
  - Treated lung tumors as systemic rather than portal-of-entry effects
- 2010 Review assumed that IUR for female mice applies to human exposure
- Applied age-dependent adjustment factor without sufficient evidence to support the incorrect mutagenic MOA
- Rounding intermediate results multiple times in the same calculation skews final result

EPA's Chloroprene URE Should Be Consistent with Similar Compounds

Chemical	IARC Group	EPA Carcinogenicity Assessment	URE
Benzene	1	"A"	2.2E-06
Vinyl chloride	1	"A"	8.8E-06
Tetrachloroethylene (TCE)	2A	"Likely"	2.6E-07
Acetaldehyde	2B	"Probable"	2.2E-06
Hexachlorobutadiene	3	"Possible"	2.2E-05

IARC Classifications:

1	Known Carcinogen	2B	Possible Carcinogen
2A	Probable Carcinogen	3	Not Carcinogenic

2010 Review Did Not Use PBPK Model

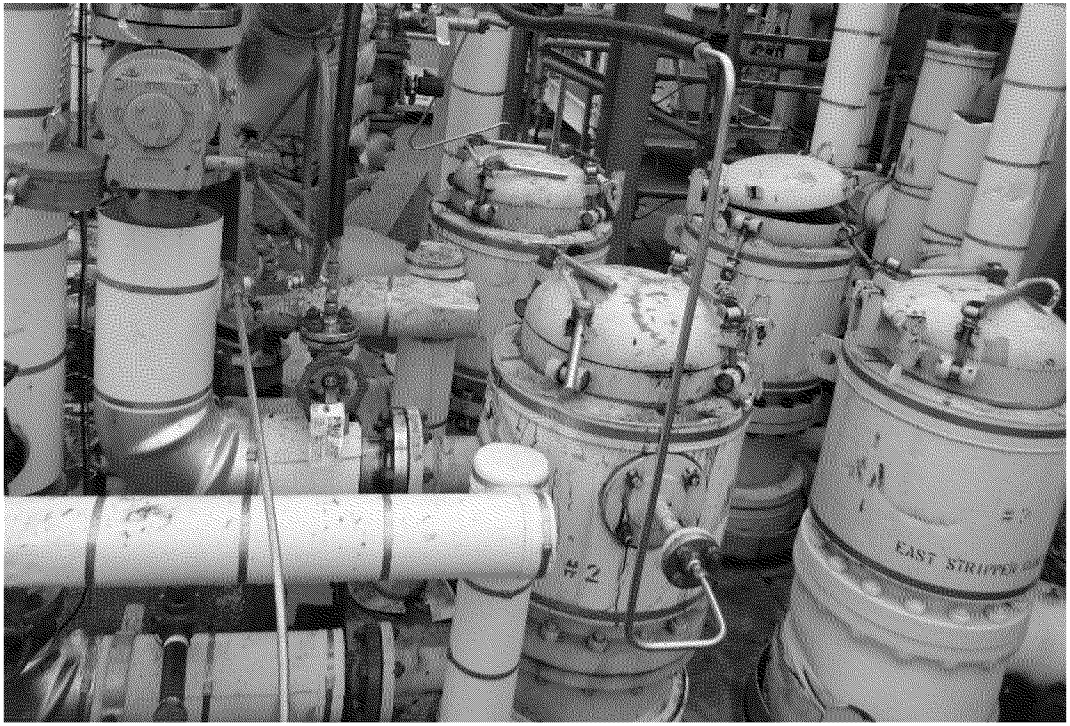
- Presented with the evidence, EPA should have used a physiologically-based pharmacokinetic (PBPK) model to extrapolate mouse toxicology data to humans
- Although a validated PBPK model (Himmelstein, 2004) was available at the time of the 2010 Review, EPA declined to use it
- Since 2010, 3 separate studies have validated the Himmelstein model
- 2010 Review even states: "Ideally, a PBPK model…would decrease some of the quantitative uncertainty in interspecies extrapolation…" (p. 141)
- Failure to use PBPK resulted in overly conservative IUR

Chloroprene is not "likely…carcinogenic"

- 2010 Review states that IRIS determined chloroprene's carcinogenicity based on the following criteria:
  1. NTP study finding early appearance of tumors
  2. Elevated liver cancer risk from occupational exposure
  3. Suggestive evidence of increased lung cancer risk from occupational exposure
  4. Proposed mutagenic mode of action
  5. Structural similarities to known carcinogens 1,3-butadiene and vinyl chloride
- RE's report shows that only 2 of these remain true
- Chloroprene carcinogenicity should be downgraded to "suggestive to be carcinogenic in humans"

Ramboll Environ's Updated IUR

- Ramboll Environ (RE) used NTP data with a PBPK model to derive a more scientifically grounded IUR
  - Applied standard EPA methodology
  - Used conservative assumptions where appropriate
- Results are consistent with other structurally similar chemicals



Ramboll Environ's Updated IUR: 3.2×10^{-6} /µg/m^3 (156-fold difference)

Appropriate Risk-based Ambient Target: 31.2 µg/m^3

10 month off-site average of 5.76 µg/m^3

AOC requires an 85% reduction

Conclusions

- IRIS' 2010 Toxicological Review of Chloroprene contains numerous deviations from accepted scientific practice
- The RFC shows that current emissions of chloroprene are well within acceptable cancer risk calculations. Installation of the RTO and other AOC-required emission reduction projects must achieve 85% emissions reduction

The 2010 Review needs to be updated

Thank you