“In the current regulatory climate, the focus on energy-curable materials needs to be tempered with an understanding of real exposures based on actual conditions of use…The focus, therefore, needs to center around managing exposures, wherever possible, rather than believing that removing substances eliminates risk.”

--Lisa Fine
Past President RADTECH
2018 Editorial UV+EB Technology

The Story: Finding a Path on an Ever-Changing Landscape

- Globally Harmonized System of Classification and Labeling of Chemical by the UN (GHS)
- REACH regulations adopted by the European Union
- TSCA Section 5(a)
  - Significant New Use Rules—requires notice to the EPA before chemical substances and mixtures are used in new ways that might create concerns.
  - Application process and inclusion could hinder innovation.

EuPIA Exclusion Policy

Policy whereby member companies agree to avoid raw materials if one or more components are listed in Group A and B of the exclusion criteria the exclusion criteria.

Criteria is defined by the hazard statement/code in the CLP.

Changes in Systems

- Led to reevaluating the hazard classifications of common chemicals
- Resulted in ink manufacturers needing to reevaluate ink formulations
- Created a need to revisit safety and exposure of employees, customers, and consumers.
Every problem has in it the seeds of its own solution

- How do we, as manufacturers, respond to an *Ever-Changing Landscape*?
- Hazard Based Solution
  - Accept a Hazard, change formula accordingly.
  - PI379 replacement
- **Risk Based Solution**
  - Assess the Risk by determining the *Actual Exposure*

The Risk Based Solution: Finding the seed of the solution within the problem.

- EuPIA Exclusion Policy also states that if there is no suitable substitution exemptions can be approved for hazards in Group A.
- For hazards in Group B, individual member companies can conduct a risk assessment to demonstrate that safe use is assured.

**PI369 reclassification by REACH Committee of the European Chemicals Agency (ECHA)**

- Category 1B: H360D; may damage the unborn child

**EuPIA Group B of the Exclusion Criteria***

*At the time of the study and writing the paper; Currently SVHC by ECHA*
Most people spend more time and energy going around problems than in trying to solve them. ~Henry Ford

- How do we
  1) Measure PI369?
  2) Quantify PI369?
  3) Relate quantity to exposure level?

The No Observed Adverse Effect Level (NOAEL) in EFSA is 100mg/kg body weight
Pregnant female (applying the average weight of 68 kg, France)

The Study Design

Arm 1

- Production Facility
- INX Edwardsville, Kansas Production Facility

  - For our study, pumps were not worn to mimic “worst case scenario”
  - We asked: Where is the worst cumulative 8-hour exposure?
  - Constant air flow pumped through the filter for collection
  - Active Air Filter—Zefon International 37 mm 3pc, cassettes; 1 um glass fiber filter

Arm 1 Results

- For the Worst-Case Sample:
  - 64 microgram (ug) PI369 / 8 hour = 0.064 mg / 8 hour

HPLC-MS/MS

- Parent Ion Positively Charged PI369: m/z = 367
- Daughter Ions m/z 367→190, 190→176
- 367
- 190
- 176

Arm 1

- Production Facility
- INX Edwardsville, Kansas Production Facility

  - Pumps were placed at fixed locations around facility:
    - “Area 1”—area away from PI weigh up and mixer—Expected to be low exposure/control
    - Flexo Mixer
    - PI Kettle
      - Continual production over trial, this is not considered a “normal production day”.

  - PI369 was extracted from the filters and analyzed by LC/MS/MS
Arm 1 Results—Perspective

- Worst case sample: 64 microgram/8 hour
- Best case sample: 1 microgram (ug) /8 hour

0.001 g = 6 g = 6000 mg
0.001 mg = 1 mg = 100 ug

Arm 1 Results

- Worst case sample: 64 microgram/8 hour
- Best case sample: 1 microgram (ug) /8 hour

0.001 g = 6 g = 6000 mg
0.001 mg = 1 mg = 100 ug

Arm 2

Simulated Press Trial

• Proof of concept study by simulating a pressroom environment using an inkometer

Distance to filter 3: 15 ft; End of table
Front: from center of rubber roller 2 ft
Back: from center of rubber roller 2 ft
1.5 sugar cubes = 6 g
1 sugar cube = 4 g

Arm 2

Simulated Press Trial

Distance to filter 3: 15 ft; End of table
Front: from center of rubber roller 2 ft
Back: from center of rubber roller 2 ft
1.5 sugar cubes = 6 g
1 sugar cube = 4 g

Arm 2

Simulated Press Trial

Distance to filter 3: 15 ft; End of table
Front: from center of rubber roller 2 ft
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1.5 sugar cubes = 6 g
1 sugar cube = 4 g

Arm 2

Simulated Press Trial

Distance to filter 3: 15 ft; End of table
Front: from center of rubber roller 2 ft
Back: from center of rubber roller 2 ft
1.5 sugar cubes = 6 g
1 sugar cube = 4 g
Arm 2 Results
- 1200 rpm roller speed
- 1-hour testing with ink replenished every 5 or 15 minutes

<table>
<thead>
<tr>
<th>Trial</th>
<th>Ink Changed Every 5 minutes</th>
<th>Ink Changed every 15 minutes</th>
<th>PI369 microgram / 8-hour day / 68 kg bdw Worst Case</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>End of Table</strong></td>
</tr>
<tr>
<td></td>
<td>0.021 (0.168)</td>
<td>0.014 (0.112)</td>
<td>0.0025</td>
</tr>
<tr>
<td></td>
<td>0.081 (0.648)</td>
<td>0.029 (0.232)</td>
<td>0.0096</td>
</tr>
<tr>
<td></td>
<td>3.391 (27.128)</td>
<td>6.262 (50.096)</td>
<td>0.7368 <strong>0.000911% of NOAEL</strong></td>
</tr>
</tbody>
</table>

NOAEL = 100mg/kg bdw
= 6800 mg / 8-hour day
= 6,800,000 microgram / 8-hour day

Arm 3 Pressroom Trial
- Pressroom Air quality trial
- Run UV inks with PI369

Pressroom Air quality trial
- Number represents filter and location
- Filters were positioned at various locations on the Print Unit

Printing Press Schematic
- Arm 3 Pressroom Trial
- Run UV inks with PI369

Front (Finish) Back (Feed)
1 10 4 7 8
2 11 5 8 9
3 12 6

Arm 3 Pressroom Trial
- Pressroom Air quality trial
- Run UV inks with PI369

Front (Finish) Back (Feed)
1 10 4 7 8
2 11 5 8 9
3 12 6

Arm 3 Pressroom Trial
- Pressroom Air quality trial
- Run UV inks with PI369

Front (Finish) Back (Feed)
1 10 4 7 8
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3 12 6

Arm 3 Pressroom Trial
- Pressroom Air quality trial
- Run UV inks with PI369

Front (Finish) Back (Feed)
1 10 4 7 8
2 11 5 8 9
3 12 6
### Arm 3 Recovery Trials

- **Recovery 75-125%**
  - PI369 in acetonitrile spotted directly onto blank filter
  - Ink containing PI369 spotted directly onto filter
- **Met accuracy (N=3) and repeatability (N=6) levels for method validation**
- **%Relative standard deviation ≤20%**

<table>
<thead>
<tr>
<th>Vendor</th>
<th>Average PI369 / gram ink</th>
<th>SEM</th>
<th>% Relative Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.035</td>
<td>0.0011</td>
<td>0.051</td>
</tr>
<tr>
<td>B</td>
<td>0.014</td>
<td>0.0005</td>
<td>0.061</td>
</tr>
<tr>
<td>C</td>
<td>0.013</td>
<td>0.0003</td>
<td>0.039</td>
</tr>
</tbody>
</table>

Norwood and Felden, 2018

### Arm 3 Results

**Microgram PI369 / 8-hour day / kg bdw**

<table>
<thead>
<tr>
<th>Location</th>
<th>Front Finish</th>
<th>Top of Press</th>
<th>Bottom of Press</th>
<th>Total PI369 as a percentage of the Level of Reasonable Certainty of No Harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Press</td>
<td>Side2</td>
<td>Side2</td>
<td>Side2</td>
<td>Press Side Top of Press Side2 Bottom of Press Side2</td>
</tr>
<tr>
<td></td>
<td>0.0024</td>
<td>0.2837</td>
<td>0.0090</td>
<td>0.00000002%</td>
</tr>
<tr>
<td></td>
<td>0.0011</td>
<td>1.4097</td>
<td>0.4299</td>
<td>0.00003%</td>
</tr>
<tr>
<td></td>
<td>0.0000063</td>
<td>1.5850</td>
<td>0.00012</td>
<td>0.0000001%</td>
</tr>
</tbody>
</table>

### How does the Number of Breaths a Day Impact Calculated Exposure

**Average Air Flow in the Filter Pump**

<table>
<thead>
<tr>
<th>At Rest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant set flow</td>
</tr>
<tr>
<td>Average flow</td>
</tr>
<tr>
<td>Ratio of Liters of air from breath to the filter pump</td>
</tr>
</tbody>
</table>

Implies a person would inhale 4.1X liters of air more than the filter
### How does the Number of Breaths a Day Impact Calculated Exposure

<table>
<thead>
<tr>
<th>Activity</th>
<th>Constant set flow</th>
<th>Average flow 94 L over 8-hour period</th>
<th>Ratio of Liters of air from breath to the filter pump</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brisk Walk</td>
<td>7-8 L of air/min</td>
<td>3840 L of air over 8-hour period</td>
<td>= 4.1</td>
</tr>
<tr>
<td>Mowing the Lawn</td>
<td>37 L of air/min</td>
<td>16800 L of air over 8-hour period</td>
<td>= 17.8</td>
</tr>
</tbody>
</table>

- Implies a person would inhale 4.1X liters of air more than the filter
- Implies a person would inhale 17.8X liters of air more than the filter

### Normalized to Rate of Breathing

<table>
<thead>
<tr>
<th>Activity</th>
<th>Front Finish (1)</th>
<th>Front Finish (2)</th>
<th>Front Finish (3)</th>
<th>Front Finish (4)</th>
<th>Back Finish (5)</th>
<th>Back Finish (6)</th>
<th>Back Finish (7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brisk Walk</td>
<td>0.0000002%</td>
<td>0.00000082%</td>
<td>0.0000034%</td>
<td>0.0003%</td>
<td>0.0012%</td>
<td>0.0053%</td>
<td>0.0053%</td>
</tr>
<tr>
<td>Mowing the Lawn</td>
<td>0.000009%</td>
<td>0.000037%</td>
<td>0.0015%</td>
<td>0.0003%</td>
<td>0.0012%</td>
<td>0.0053%</td>
<td>0.0053%</td>
</tr>
<tr>
<td>Assumed 68 kg woman</td>
<td>0.0000001%</td>
<td>0.00000041%</td>
<td>0.0000018%</td>
<td>0.0000001%</td>
<td>0.00000041%</td>
<td>0.0000018%</td>
<td>0.0000018%</td>
</tr>
</tbody>
</table>

### What’s safe? Generally Recognized As Safe (GRAS)

- To be considered GRAS:
  - The use of the substance must meet the same safety standard as a food additive: there must be a level of reasonable certainty of no harm under the conditions of its intended use; and
  - The use of the substance must meet the general recognition standard: the intended use of the substance in food must be recognized as safe by qualified experts based on publicly available scientific information.

### Toxicological Report

- Independent Toxicologist recommended an exposure level for “Reasonable Certainty of No Harm”
  - NOAEL 100 mg/kg/day
  - Extrapolates animal data to safe levels in humans
  - Divided by 10 for intraspecies difference
  - Divided by 10 for interspecies difference
  - Divided by 3 for lack of database completeness

### Perspective...Moderate Activity

- Percentage of the Level of Reasonable Certainty of No Harm: 330 microgram / day / kg bdw

- Assumed 68 kg woman

### Perspective...Moderate Activity

- Percentage of the Level of Reasonable Certainty of No Harm: 330 microgram / day / kg bdw

- March in place for 8 hours
Finding a Path in an **Ever-Changing Regulatory Climate**

_One Under Constant Flux_

**Look Backward, Live forward:**
- Navigate changes by **applying** established methods
- Resulting in **improved** and **quicker** responses to changes

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“Exercise Prudent Avoidance”

“In the current regulatory climate, the focus on energy-curable materials needs to be tempered with an understanding of real exposures based on actual conditions of use...The focus, therefore, needs to center around managing exposures, wherever possible, rather than believing that removing substances eliminates risk.”

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How does the Number of Breaths a Day Impact Calculated Exposure

- **Active Filter pumps:**
  - Average airflow of the filter pumps = 941 L
  - Estimated breaths at rest: 7 - 8 L of air / minute
  - Ratio of Liters of air a person breaths at rest to the filter pumps = 4.1
    - This implies at rest a person would inhale 4.1X more Liters of air than the filter, or 4.1X greater PI\textsubscript{369} than the filter
  - Estimated breaths during a moderate level of activity: 35 L of air /min
    - 16800 Liters over an 8-hour day with moderate activity
    - Ratio of Liters of air a person breaths during moderate activity to the filter pumps = 17.8
    - This implies during moderate activity a person would inhale 17.8 X more Liters of air than the filter, or 17.8X greater PI\textsubscript{379} than the filter

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What does this mean for Exposure?

- Ability to go beyond **Modeling**
  - Modeling is Predictive
- In the **Ever-Changing Landscape**
  - Changing Global Markets—Supply chain changes
  - Regulatory Changes
- Determine and create **benchmarks**
  - Assess Actual Hazards
  - Assess Actual Risks in a **Real-World Setting**
  - Do so in a multi-factorial, multi-site study

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Acknowledgements

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PI Comparison

**PI\textsubscript{369}**

**PI\textsubscript{379}**