

Exposure Risk Assessment: Production to Pressroom UV Misting Exposure Study

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“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

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

- Globally **H**armonized **S**ystem 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.

https://www.unesco.org/trans/danger/publi/ghs/ghs_welcome_e.html

https://ec.europa.eu/regulation/reach/understanding_reach

<https://www.epa.gov/reviewing-new-chemicals-under-toxic-substances-control-act-tsca/actions-under-tsca-section-5>

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

- California Proposition 65—**Prop 65**
 - Has grown to over 900 chemicals
 - **Acetaminophen**—Hearings for inclusion
 - “Inclusion of a chemical on the Prop 65 list does not ban it...rather the law requires a clear and reasonable warning”
- Global Markets
 - Supply Chain
 - Country of Origin
 - Synthetic and Manufacturing Processes



California Proposition
65 Warning
WARNING: This product contains chemicals known to the State of California to cause cancer, and birth defects or other reproductive harm.
For more information: www.P65warnings.ca.gov

Ubiquitous Signage

<https://oehha.ca.gov/proposition-65>

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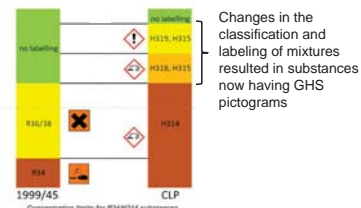


The Story: Finding a Path on an Ever-Changing Landscape

- 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.

EuPIA Exclusion Policy European Printing Ink Association

- 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*.



Group A	Group B
Acute Toxicity Cat. 1&2 [H300, H310, H330]	Acute Toxicity Cat. 3 (oral, dermal) [H301, H311]
Acute Toxicity Cat. 3 (inhalation) [H331]	
Carcinogen or Mutagen Cat. 1A & 1B [H350, H340]	Toxic to Reproduction Cat. 1A & 1B [H360] (if threshold exists)
Toxic to Reproduction Cat. 1A & 1B [H360]	STOT Repeated Exposure Cat. [H372]
STOT Single Exposure Cat. 1 [H370]	

*Classification, Labeling, and Packaging of substances and mixtures EC 1272/2008

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Nestlé Guidance, EuPIA Exclusion Policy, Swiss Ordinance, TSCA, Prop 65

- It is **foreseeable** that lists will change and evolve
- Think Globally



K Kazarian, Packaging Strategies, 2019

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Nestlé Guidance, EuPIA Exclusion Policy, Swiss Ordinance, TSCA, Prop 65

- It is **foreseeable** that lists will change and evolve
- Think Globally

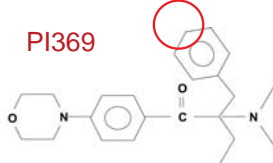
RANK	COMPANY & HEADQUARTERS	KEY BRANDS	2018 TOTAL REVENUE (IN U.S. \$B)
1	Nestlé, Vevey, Switzerland	Nestlé, Nescafé, Purina, Dreyer's, Stouffer's, Nestlé, Lean Cuisine, Perrier, Nesquik, Nescafé, Nestlé Pure Life, S. Pellegrino	93.40
2	PepsiCo, Purchase, NY	Lay's, Quaker, Doritos, Ruffles, Tostitos, Fritos, Pepsi, Garden of Eatin', Aquafina, Mountain Dew, Sprite, Naked, Starbucks RTD	65.00
3	Anheuser-Busch InBev, Leuven, Belgium	Beck's, Bud Light, Corona, Stella Artois, Beck's, Modelo Especial, Michelob Ultra	54.60
4	JBS, Greeley, CO	Swift, Cedar River Farms, Pilgrim's Pride	49.70
5	Tyson Foods, Springdale, AR	Tyson, Wright, Jimmy Dean, Hillshire Farm, Sara Lee, Ball Park	40.00
6	Mars International, Macclesfield, Virginia	M&M's, MilkyWay, Dove, Skittles, Whitaker, Uncle Ben's, Pedigree, Royal Canin	35.00
7	Coca-Cola, Atlanta, GA	Coca Cola, Powerade, Fanta, Dasani, Odwalla, Minute Tapioca, Minute Tapioca, Sprite, Clearlake smartwater	31.70
8	Cargill, Minneapolis, MN	Swirlin Shire, Bumble, Diamond Crystal, Truvia, Angus Pride	30.40

K Kazarian, Packaging Strategies, 2019

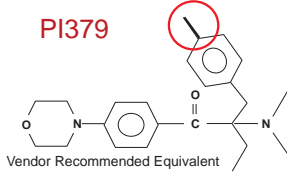
Every problem has in it the seeds of its own solution

- 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**

PI369



PI379

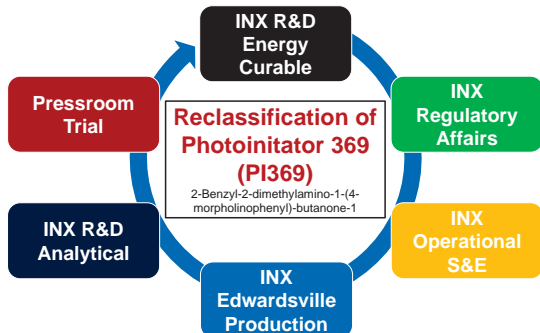


<https://echa.europa.eu/substance-information/-/substanceinfo/100.100.600>
<https://echa.europa.eu/registry-of-svhc-intentions/-/distlist/details/0b0236e183ae60b7>

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.

Risk Assessment



VISION

The destination a fixed point to which we focus all effort

- 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



<https://echa.europa.eu/substance-information/-/substanceinfo/100.100.600>

<https://echa.europa.eu/registry-of-svhc-intentions/-/distlist/details/0b0236e183ae60b7>

SVHC: Substance of Very High Concern

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?

INX Operational S&E

INX R&D Analytical

INX Regulatory Affairs

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

Production Facility

Arm 1: Determine the exposure by monitoring the air quality in a production facility.



Simulated Press Trial

Arm 2: Proof of concept study: Simulate a pressroom using an inkometer. Measure air quality.



Pressroom Trial

Arm 3: Measure air quality in a press trial. Run UV inks with PI369.

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

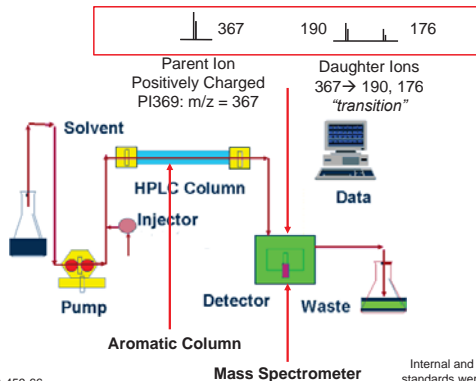


Arm 1 Production Facility

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

HPLC-MS/MS



Gallart-Ayala H et al. J.Chrom.A 1218(2011) 459-66

Arm 1 Results



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

NOAEL in EFSA is 100mg/kg body weight → 6800 mg / day for a 68 kg female

- What does this tell us?
 - Proof of concept for method
 - Amount detected near PI Kettle and mixer is below the NOAEL

Arm 1 Results—Perspective

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



Arm 1 Results

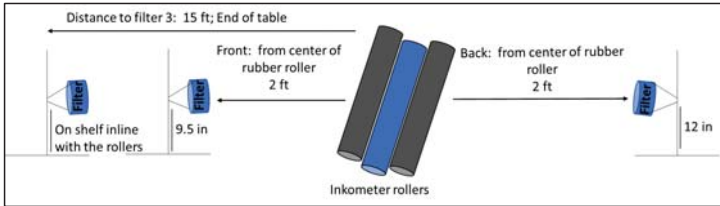
- Worst case sample: 64 microgram/8 hour
- Best case sample: 1 microgram (ug) /8 hour



Arm 2

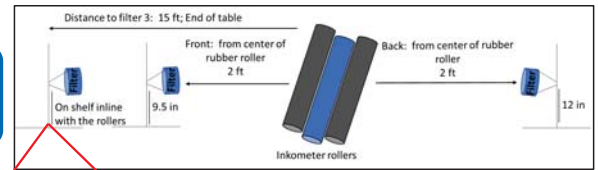
Simulated Press Trial

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



Arm 2

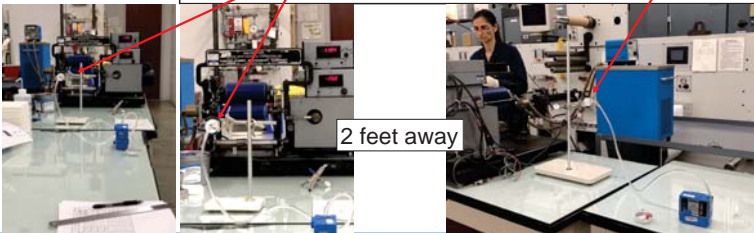
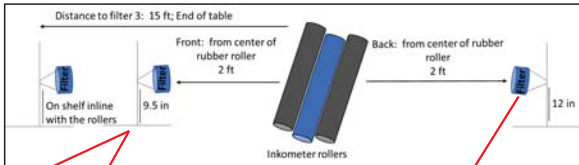
Simulated Press Trial



15 feet away

Arm 2

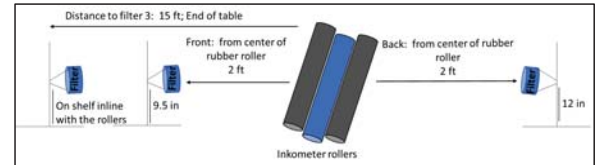
Simulated Press Trial



2 feet away

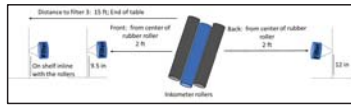
Arm 2

Simulated Press Trial



Arm 2 Results

- 1200 rpm roller speed
- 1-hour testing with ink replenished every 5 or 15 minutes



Trial	Ink Changed Every 5 minutes	Ink Changed every 15 minutes	PI369 microgram / 8-hour day / 68 kg bdw Worst Case
	Microgram PI369 collected / filter 1-hour trial (8-hour trial)		
End of Table	0.021 (0.168)	0.014 (0.112)	0.0025
Front, 24 inches from the middle of the roller	0.081 (0.648)	0.029 (0.232)	0.0096
Back, 24 inches from the middle of the roller	3.391 (27.128)	6.262 (50.096)	0.7368

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

0.000011% of NOAEL

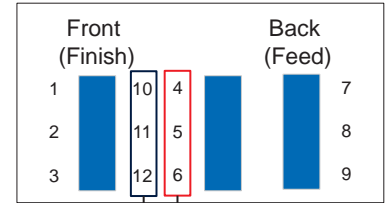
Arm 3

Pressroom Trial

- Pressroom Air quality trial
- Run UV inks with PI369

Printing Press Schematic

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

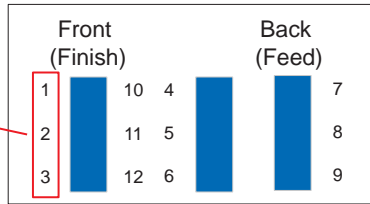


Bottom of Press ← → Top of Press

Arm 3

Pressroom Trial

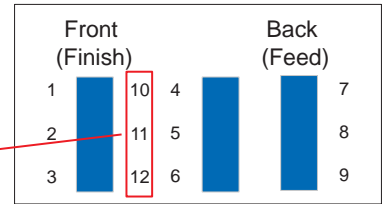
- Pressroom Air quality trial
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Arm 3

Pressroom Trial

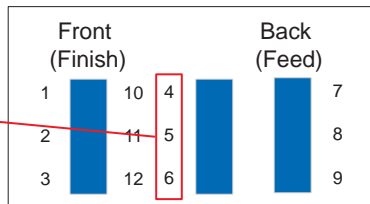
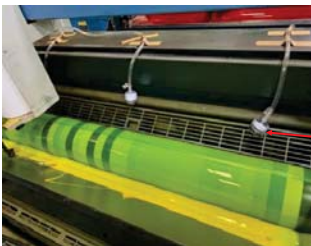
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Arm 3

Pressroom Trial

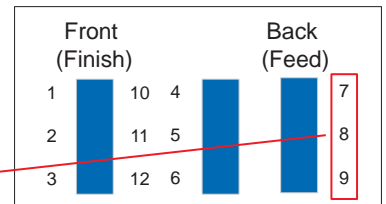
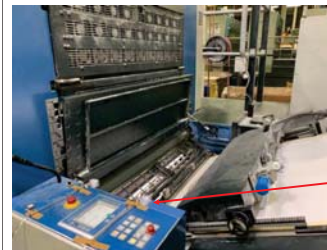
- Pressroom Air quality trial
- Run UV inks with PI369



Arm 3

Pressroom Trial

- Pressroom Air quality trial
- Run UV inks with PI369



Variables worth noting

- 3 press trials over three different days
- 3 ink companies' inks
 - Where only the INX formula was known
- Analysis for only PI369, no other UV material was quantified
- Pumps were turned off when press was idle (max risk assessment)
- 3 different print units
- The press trial was conducted during other press runs.
 - 1 of 3 press units
- Various Press Speeds

Arm 3 Recovery Trials

- Recovery 75-125%*
 - PI369 in acetonitrile spotted directly onto blank filter
 - Ink containing PI369 spotted directly onto filter
- Met accuracy ($N \geq 3$) and repeatability ($N \geq 6$) levels for method validation
- %Relative standard deviation $\leq 20\%$
- Neat samples provided were extracted and quantified for the content of PI369

Vendor	Average gram PI 369 / gram ink	SEM	%Relative Standard Deviation
A	0.035	0.0011	0.051
B	0.014	0.0005	0.061
C	0.013	0.0003	0.039

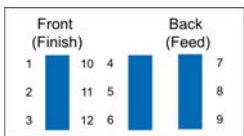
Norwood and Feilden, 2018*

Arm 3 Terms

Press Location	Total Per Filter microgram / day / kg bdw	Total Microgram / day / kg bdw as a Percentage of the Level of Reasonable Certainty of No Harm	PPB Extrapolated (8 hours)	Press Location	Average total microgram / day / kg bdw	Total Microgram / day / kg bdw as a Percentage of the Level of Reasonable Certainty of No Harm	PPB Extrapolated (8 hours)
Front Finish	0.00006 0.00046	0.000017 0.000140	0.00027 0.00218		0.3185 0.0320	0.096501 0.09687	1.50483 0.16785
Filters Categorized and Averaged by Placement				Total PI369 as a percentage of the Level of Reasonable Certainty of No Harm			
	0.5354	0.162253	2.59504	Back of Press side	0.00001	0.00004	0.00006
Average Total PI369 normalized to hours and body weight				PPB: measure of air concentration over 8 hours			
Top of Press	0.0405	0.012277	0.03125	Bottom of Press middle	0.0134	0.004050	0.06316
Press Middle	0.0066	0.002004	0.02242	Bottom of Press side	0.0154	0.004669	0.07281
	0.0049	0.001473	0.02242		0.0099	0.003015	0.04821
	0.2344	0.071025	1.32333				
	0.2730	0.082740	1.32333				
	0.0079	0.002407	0.03753				

Arm 3 Terms

Press Location	Total Per Filter microgram / day / kg bdw	Total Microgram / day / kg bdw as a Percentage of the Level of Reasonable Certainty of No Harm	PPB Extrapolated (8 hours)	Press Location	Average total microgram / day / kg bdw	Total Microgram / day / kg bdw as a Percentage of the Level of Reasonable Certainty of No Harm	PPB Extrapolated (8 hours)
Front Finish	0.00006 0.00046	0.000017 0.000140	0.00027 0.00218		0.3185 0.0320	0.096501 0.09687	1.50483 0.16785
No Observed Adverse Effect Level (NOEL) = 100 milligram/ day /kg bdw							
	0.00019	0.000057	0.00089	Back of Press side	0.00001	0.00004	0.00006
Level of Reasonable Certainty of No Harm = 330 microgram / day / kg bdw							
Top of Press	0.0405	0.012277	0.03125	Bottom of Press middle	0.0134	0.004050	0.06316
Press Middle	0.0066	0.002004	0.02242	Bottom of Press side	0.0154	0.004669	0.07281
	0.0049	0.001473	0.02242		0.0099	0.003015	0.04821
	0.2344	0.071025	1.32333				
	0.2730	0.082740	1.32333				
	0.0079	0.002407	0.03753				



Arm 3 Results

	Microgram PI369 / 8-hour day / kg bdw *	PPB PI369	Total as a Percent NOEL Limit NOEL = 100 mg / day / kg bdw
Front Finish (1)	0.00024	0.0011	0.0000002%
Top of Press, Side (4)	0.2837	1.4097	0.0003%
Bottom of Press, Side (10)	0.3318	1.6335	0.0003%
Top of Press, Middle (5)	0.0890	0.4259	0.00009%
Bottom of Press, Middle (11)	0.3225	1.5850	0.0003%
Back Feed, Side (7)	0.00012	0.00063	0.0000001%

How does the Number of Breaths a Day Impact Calculated Exposure

Average Air Flow in the Filter Pump	At Rest
Constant set flow	7-8 L of air / min
Average flow 941 L over 8-hour period	3840 L of air over 8-hour period
	Ratio of Liters of air from breath to the filter pump = 4.1
	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

Average Air Flow in the Filter Pump	At Rest	At Moderate Activity
Constant set flow	7-8 L of air / min	37 L of air / min
Average flow 941 L over 8-hour period	3840 L of air over 8-hour period	16800 L of air over 8-hour period
	Ratio of Liters of air from breath to the filter pump = 4.1	Ratio of Liters of air from breath to the filter pump = 17.8
	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

Moderate Activity:



Brisk Walk



Mowing the Lawn

		Normalized to Rate of Breathing		
		Total as a Percent NOAEL Limit NOAEL = 100 mg / day / kg bdw	A Person At Rest Over 8 Hours 4.1 X	A Person During Moderate Activity Over 8 Hours 17.8X
Assuming 68 kg woman	Front (Finish)			
	1	10	4	7
	2	11	5	8
	3	12	6	9
	Back (Feed)			
	7			
	Front Finish (1)	0.0000002%	0.00000082%	0.0000034%
	Top of Press, Side (4)	0.0003%	0.0012%	0.0053%
	Bottom of Press, Side (10)	0.0003%	0.0012%	0.0053%
	Press Top of Press, Middle (5)	0.00009%	0.00037%	0.0015%
	Bottom of Press, Middle (11)	0.0003%	0.0012%	0.0053%
	Back Feed, Side (7)	0.0000001%	0.00000041%	0.0000018%

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

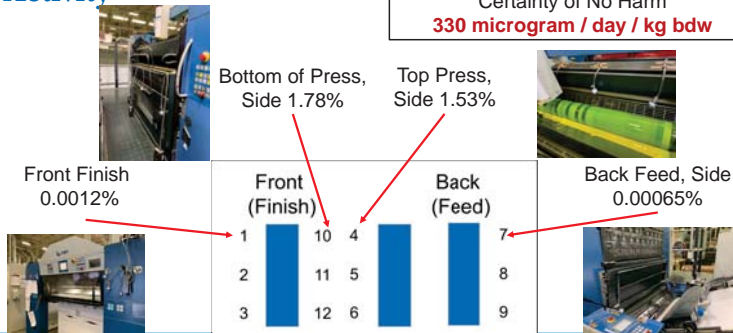
INX Regulatory Affairs

- 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

330 microgram / kg / day

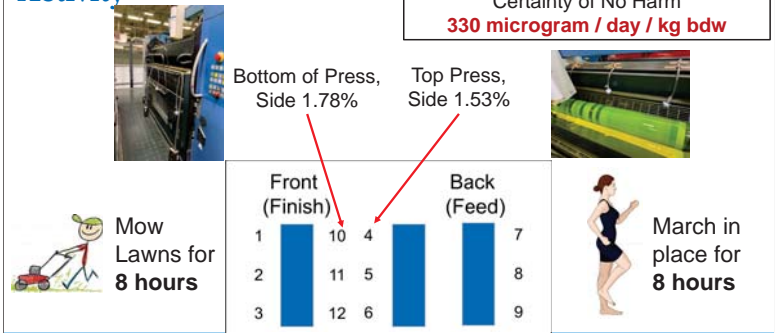
Perspective...Moderate Activity

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



Perspective...Moderate Activity

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



Life can only be understood backwards; but it must be lived forwards... S. Kierkegaard

- We have the data, now what do we do with it?
 - **So What?**

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

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

Effective decision making on PPE requirements

Improved safety for employees and customers

“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.”

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

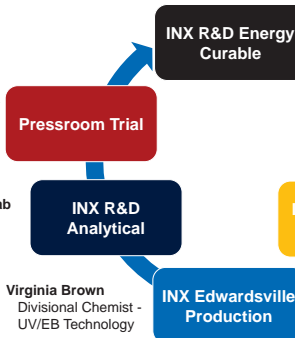
Acknowledgements



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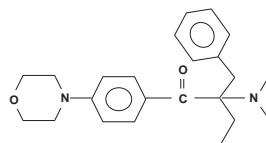
Mike Loncar
Lab Manager

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
 - 3840 Liters over an 8-hour period
 - 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 PI369 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 PI369 than the filter

PI Comparison

PI369



PI379

