Exposure Risk Assessment: Production to Pressroom

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Abstract

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Abstract

In a regulatory climate which undergoes continual changes, manufacturers are presented with the dilemma on how to respond efficiently to reclassifications of UV ink raw materials. The reclassification of PI369, as a reproductive toxin and subsequently updated by the European Union as a Substances of Very High Concern, illuminates a situation where the focus of the regulatory climate is largely centered around the hazards of raw materials rather than risk and exposure. The current paper evaluates the misting exposure in a production facility, a proof of concept inkometer study and at a printing facility.

Introduction

Systems employed to improve and protect human health and the environment, the Globally Harmonized System of Classification and Labelling of Chemicals, by the United Nations, (GHS) and REACH, regulations adopted by European Union, have changed the hazard classifications of many chemicals and commonly used UV printing raw materials. The changing reclassifications required and continues to require ink manufacturers to reevaluate ink formulations as well as revisit the safety of use and exposure to employees, customers, and consumers.

In response to reclassifications, INX chose to study the actual exposure of a common photoinitiator which was reclassified by REACH committee of the European Chemicals Agency (ECHA) as toxic for reproduction, Category 1B (H360D; may damage the unborn child). The photoinitiator, 2-Benzyl-2-(dimethylamino)-1-[4-(4-morpholinyl)phenyl]-1-butanone (PI 369; CAS119313-12-1; EC404-360-3), was reclassified from Repr. 2 H361 to Repr. 1B H360d, meaning exposure is a

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concern for pregnant female workers. The ECHA scientific overview for PI369 identified the no observed adverse effect level (NOAEL) to be 100 mg/kg body weight/day. Because PI369 is classified as a reproductive toxin, the average mass of a pregnant female in France is used for body weight (68 kg). The mass of a pregnant female in France is the lowest average reported mass. For this risk assessment where exposure is reported per body mass, the current results reflect the worst-case scenario exposure levels. Additionally, subsequent toxicology report commissioned by INX Regulatory Affairs concluded that the level of reasonable certainty of no harm to be 0.330 mg/kg body weight/ day. Reclassification of chemicals falls within the scope of the European Packaging Ink Association (EUPIA) Exclusion Policy. Subsequently, PI369 was added to the list. The Exclusion Policy states that "substances and mixtures in stated hazard classes are ***excluded*** as raw materials for the manufacture of printing inks". The Exclusion Policy is largely based on hazard classification as opposed to risk assessment studies which would detail actual daily exposure. Recent reclassification of PI369 gave EUPIA member companies six months to reformulate away from PI369 (starting March 22, 2018) (ECHA, Committee for Risk Assessment, Annex 1, 2016). An exemption can be filed for continue use, until the component of concern (PI369) is reclassified as a Substance of Very High Concern (SVHC).

The purpose of this study was to determine the actual risk-based exposure to the common PI over the course of an 8-hour period. To determine the actual exposure-based risk of PI369, an air quality trial was undertaken to evaluate and quantify the exposure of PI369 to individuals handling it and/or working in a facility where it is used. Knowing the NOAEL and the reasonable certainty level of no harm, allows for direct comparisons of exposure in a "real-world" risk assessment study in an ink production facility and pressroom.

The risk assessment was a coordinated effort between INX Operational Health and Safety Group, INX R&D Analytical, and INX R&D Energy Curable labs. Active air sampling pumps were used to collect and test for PI369 in each of three arms of this study. The first arm of the project assessed air quality in at various locations in an ink production facility to examine air quality where the PI is used. The second arm of the study was to provide proof of concept for testing the air quality in a pressroom. A press trial simulation was run using an inkometer to create misting of UV ink and the air quality was assessed and analyzed for the PI. The pressroom trial was the third arm of the project to assess the risk of exposure to pressroom workers. In the pressroom trial, active sample pumps were set up at various locations around a press—near the ink rollers, expected to be a worst-case exposure area as well as by the control booth, expected to be the area of least exposure. In each arm of the study, areas of the worst (highest) exposure and least exposure were identified.
The air filters were extracted and subsequently quantified for PI369 content by liquid chromatography tandem mass spectrometry. The analysis was consistent with quantitation and validation methods criteria set forth by the USFDA. At constant

flow through the filter, the analysis revealed that the filter with the highest content of IPI369, or worst-case exposure where the filter was located near the rollers. Average PI369 detected on the filters was 0.00024 microgram / 8-hour day/ kg bdw (equivalent to 0.0003% NOAEL).

This technical paper is the culmination of the three projects which provides data for the current risk assessment of PI369. Equally important, this study provides a framework for future exposure testing for other chemicals. Additionally, risk-based assessments provide better information to companies for requirements of personal protective equipment (PPE). Global markets for chemicals and raw materials in ink manufacturing is continuously changing. Following an explosion at a chemical plant in March 2019, the production of key intermediates and photoinitiators is expected to be affected due to efforts by the Chinese government to improve safety conditions (Bloomberg, 2019). The ability of ink manufacturers to make production and formulation decisions based on the actual risk to employees and customers, as opposed to making decisions based on perceived risk or hazard, can potentially allow for more efficient allocation of scarce materials. As the global supply of raw materials change and safety and toxicology data become available, it is becoming more important to determine actual exposure and risk, determine and create benchmarks for exposure.

Experimental Methods

Air Quality Testing

Ink Production Facility
Zefon filters (37 mm, piece) were used with SGS Galson active flow meters for constant air flow pump for collection. Two filters were set in three locations and left for 8 hours during the collection. The placement of the filters is stationary, not worn by employees. Stationary placement reflects a worst-case scenario location for constant exposure over the entire time of collection. The locations were chosen for likely exposure to the photoinitiator (PI) 369:

1) near the MFG Vessel
2) near a flexo mixer
3) low exposure area away from the mixer and PI kettle, considered a control.

Simulated Press Trial
SGS Galson active flow meters with filters were placed near an inkometer during 60-minute trials (Figure 1). One filter was placed 24 inches from the front of the center roller while a second filter was placed 24 inched from the center of the back roller. These two filters were placed to simulate a worst-case scenario exposure to UV ink misting from a press. The third was placed 15 feet from the inkometer to simulate the distance from the press to the press control booth. Notably, the

inkometer rollers were not covered during the trial, which allowed for maximal misting into the air.

On a press, ink is continually being added to the rollers. To simulate this and reduce drying out or slinging of ink, the rollers were cleaned, and new ink was added every 5 minutes for trial 1 and every 15 minutes for trials 2 and 3. The trials were run for a total of 60 minutes uptime.

While the misting trial using an inkometer does not completely simulate the same misting conditions experienced while using a printing press, all efforts were made to replicate worst case scenario conditions of UV ink misting exposure on a printing press.

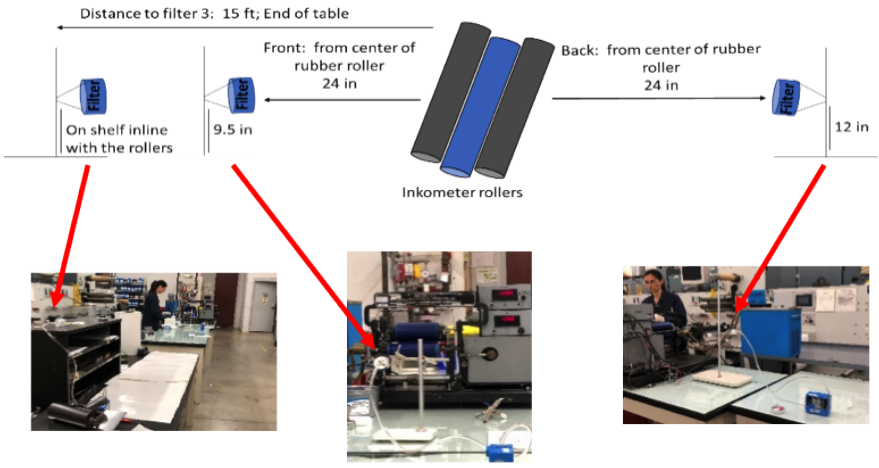


Figure 1. *Schematic of filter placement with respect to the inkometer rollers. Pictures below show actual filter placement.*

Pressroom Trial

GS Galson active flow meters with Zefon filters were placed according to Figure 2. The press trial took place over three separate days, comparing multiple presses and filter placement on each press.

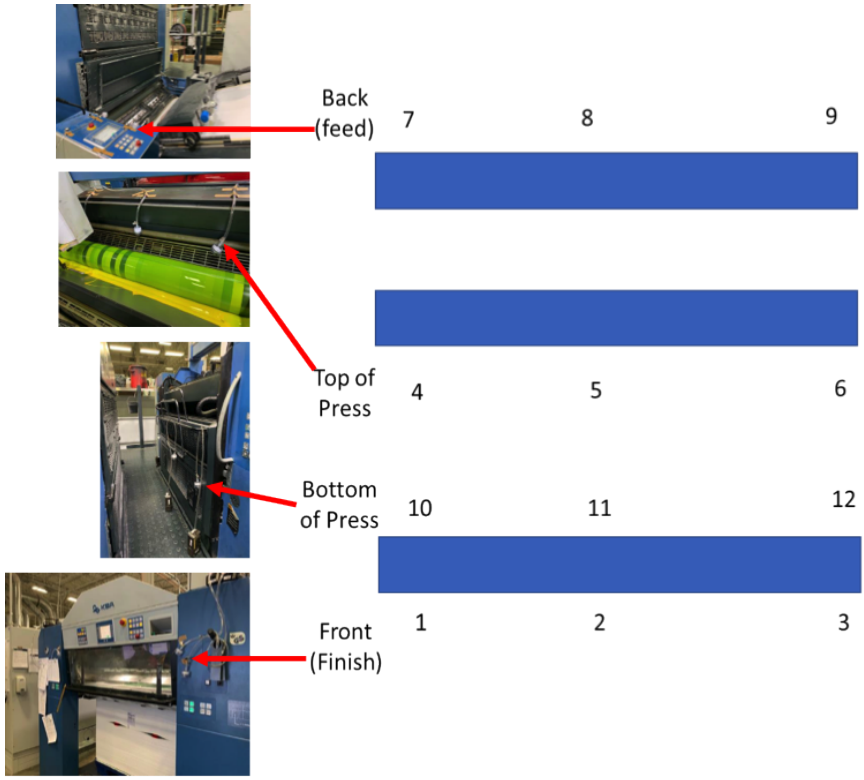
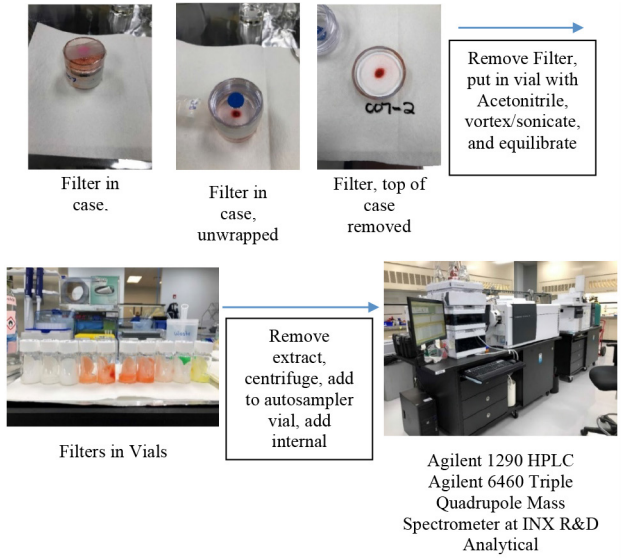


Figure 2. *Schematic of filter placement on the press unit. Numbers indicate filter and location. Pictures show actual placement during trial.*

Extraction

The filters were carefully removed and put in a 20 mL glass vial. Four milliliters of acetonitrile were added to the vial. The vials were vortexed for 30 seconds and allowed to sit for 30 minutes prior to removing the acetonitrile for centrifugation. The acetonitrile extract was removed and centrifuged to remove any fibers or particles from the filter. The supernatant was removed for analysis and put in an amber vial for storage in the refrigerator (Schematic 1).



Schematic 1. *Schematic of workflow from the wrapped filter as received by INX R&D Analytical to analysis by LC/MS/MS.*

Detection Method

The filters were carefully removed and put in a 20 mL glass vial. Four milliliters of acetonitrile were added to the vial. The vials were vortexed for 30 seconds and allowed to sit for 30 minutes prior to removing the acetonitrile for centrifugation. The acetonitrile extract was removed and centrifuged to remove any fibers or particles from the filter. The supernatant was removed for analysis and put in an amber vial for storage in the refrigerator (Schematic 1).

Fresh calibration standards were prepared including an internal standard of thioxanthen-9-one. Sample extracts were separated using a Restek Biphenyl LC Column (2.1 x 50 mm; 2.7 microm) on an Agilent 1290 HPLC. Photoinitiators and UV material was detected by multiple reaction monitoring (MRM) on an Agilent 6460 Triple Quadrupole Mass Spectrometry (QqQ). For MRM, the instrument scans for the presence of a molecular ion, applies a voltage to fragment the ion into smaller parts. Positive identification by MRM occurs by detection the transition of the molecular ion and fragments. Separation and detection were previously optimized for this system (method modified from Gallart-Ayala, et al. 2011). Internal and external standards were employed to reduce the effect of sample matrix and to quantify the amount of analytes present. MRM detection is employed to increase the selectivity of detection and eliminate influence of compounds present in the sample matrix which are not of interest.

Specifically, for PI369, the QqQ was set to search for the molecular ion, 367, and two fragments (367→190; 367→176). The 367→ 190 transition is used for quantifying content. All data reported is calculated from 367→190.

Sample extract dilutions (1X, 5X and 10X dilution) were analyzed by LC/QqQ by multiple injections ($N \geq 5$) and data represents the average quantified amount over the dilutions.

Results

Ink Production Facility

The purpose of the first arm of the study was to mimic a worst-case scenario case study. The pumps were not worn, rather they were put in a fixed location for the duration of the 8-hour exposure trial to. During the two-day trial, both the Flexo Mixer and PI kettle were in use. On a typical production day, either the flexo mixer or the PI kettle is in use. However, for the purposes of this study and to mimic a worst-case scenario, both the flexo mixer and PI kettle were in use for the duration of the trial.

Data from the 8-hour trial is reported in Table 1. PI369 was detected in all filters at differing levels. The Area 1 filter was positioned between PI racks with close proximity to the PI kettle and mixers. While not a true background, this location was equivalent to that of minimum exposure while the mixer and PI kettle are locations of "worst case scenario" exposure. The amount of PI detected in an 8-hour trial ranged from 0.09 microgram to 64 micrograms. The worst-case scenario location of near the flexo mixer was less than the NOAEL for a pregnant female. Over an 8-hour exposure trial, 64 micrograms (0.068 mg) was detected on the filter near the flexo mixer (Table 1).

Filter	Microgram / filter over 8 hours	Microgram / filter over 8 hours / kg bdw
Area 1	0.29	0.004
Area 1	0.09	0.001
Flexo Mixer	64.34	0.946
Flexo Mixer	38.13	0.561
PI Kettle	15.19	0.223
PI Kettle	39.00	0.574

Table 1. *Total PI369 detected over an 8-hour period. Adjusting for the average body weight of a pregnant female (68 kg for a pregnant female, France).*

Simulated Press Trial

The simulated press trial was a proof of concept study to quantify exposure to PI360 from misting of an inkometer. Data from the three 60-minute trials are reported in Table 1. The data reported reflects an extrapolation to an 8-hour workday. While, PI369 was detected in all filters at differing levels, the levels detected were significantly less than the NOAEL reported in the ECHA risk assessment (100 mg/kg bodyweight/day). In fact, total exposure in the worst-case scenario locations did not exceed 0.000011% of the NOAEL (0.7368 microg/kg bodyweight/day) (Table 2).

Filter Location	Location Simulating	Microgram / filter over 8 hours	Microgram / filter over 8 hours / kg bdw	PI369 microgram / 8-hour day/ 68 kg bdw Worst case
End of Table	Location Near the Controls	0.021 (0.168)	0.014 (0.112)	0.0025
Front, 24 inches from the middle of the roller	Location near the Rollers	0.081 (0.648)	0.029 (0.232)	0.0096
Back, 24 inches from the middle of the roller	Location near the Rollers	3.391 (27.128)	6.262 (50.096)	0.7368 → 0.000011% of the NOAEL

Table 2. *Total PI369 detected over a 1-hour inkometer test with a roller speed of 1200 rpm. Numbers in parentheses represent data extrapolated to an 8-hour period. The worst-case scenario location is 0.000011% of the NOAEL, 100 mg/ 8-hour day / 68 kg bdw.*

Pressroom Trial

Following the proof of concept inkometer study, a pressroom trial was set to determine PI369 in a "real world" setting. Over three days, misting exposure was tested. During the trial, active filters were positioned around a press unit as described in Figure 2. It is important to note that while the pressroom had 3 presses running, only one press unit had filters positioned for active collection.

Filter Location	Microgram / filter over 8 hours/ kg bdw	PPB	Total PI369 as a Percent of NOAEL Limit
Front Finish (1)	0.0002	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%
Tope of Press Middle (5)	0.089	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%

Table 3. *Total PI369 detected over an 8-hour pressroom trial.*

Impact of breaths per day on calculated exposure

The constant flow on the air pumps equated to an average flow rate of 941 L for air over an 8-hour period. At rest a person breaths 7-8 L of air / min, equating to 3840 L of air over 8 hours. This is 4.1 times greater than the average flow rate for the pumps. During moderate activity, that of a brisk walk or mowing the lawn, a person will breath 37 L of air/min. Over 8 hours, this equates to breathing in 16800L of air or 17.8 times more air than the flow of the air filters.

In order to determine whether the exposure us harmful, we must have a benchmark quantity considered to be safe and the exposure of PI369 needs to be normalized to the rate of breathing. The INX Regulatory Affairs commissioned a report from an independent toxicologist to recommend a quantity of PI369 that would be recognized as safe. The independent toxicologist recommended an exposure level of "Reasonable Certainty of No Harm" equal to 330 microgram / kg / day. The level for Reasonable Certainty of No harm is an extrapolation of animal data to safe levels in humans. Normalizing the experimentally determined exposure levels for breathing during moderate activity and as a percentage of the level for reasonable certainty of no harm is consistent with data from the first two arms of the study. Exposure levels from the press room trial are well below the NOAEL and the level of reasonable certainty of no harm. Figure 3 shows filter placement with the exposure level normalized to moderate activity as a percentage of the level of reasonable certainty of no harm. These exposure levels are equivalent to marching in place for 8 hours at this location of the filter. For both the back feed and front finish, the exposure is well below the level of reasonable certainly of no harm. Even locations in close proximity to the roller results in misting exposure to PI369 less than 2% of the level of reasonable certainty of no harm.

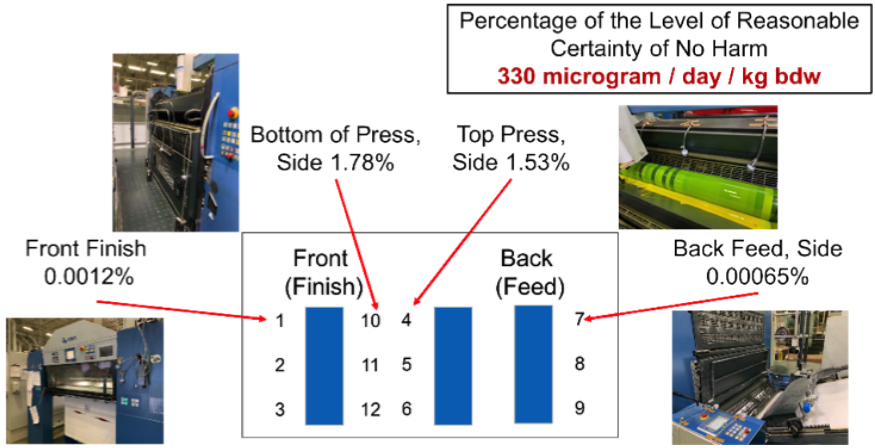


Figure 3. *PI369 exposure normalized to the average rate of breathing during moderate activity reported as a percentage of the level of reasonable certainty of no harm.*

Conclusion

The results clearly show that even under worst case scenario conditions, PI369 exposure is well below the NOAEL and level of reasonable certainty of no harm. The decision to reclassify PI369 as a substance of very high concern (SVHC) by the ECHA was largely hazard based. Consequently, the reclassification has resulted in requiring ink companies to reformulate away from using PI369. This study demonstrates the successful use of experimental methods to evaluate misting exposure. The regulatory climate is continually undergoing changes and under constant flux, as chemicals undergo reclassification. An every-changing regulatory climate creates a need for methods that can quickly be adapted and applied for other chemicals. Having established methods provide for improved and quicker responses to regulatory change. Computer modeling is a powerful tool. However, high throughput screening may not adequately account for metabolism or issues like chemical volatility (Adler and Shelton Davenport, 2010; NASEM, 2018). Due to its predictive nature, computer modeling should be followed by correlative assays, when possible. Having experimental methods which are easily adapted to test new chemicals of concern will provide the ability to assess actual hazards and actual risks in a real-world setting. This ability to respond quickly to changes will provide more effective decision making on PPE requirements which will in turn will improve safety for employees and customers.

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