 DOI: 10.1111/risa.13366

Health Risk Assessment of Photoresists Used in an Optoelectronic Semiconductor Factory

Shao-Zu Huang and Kuen-Yuh Wu*

Photoresist materials are indispensable in photolithography, a process used in semiconductor fabrication. The work process and potential hazards in semiconductor production have raised concerns as to adverse health effects. We therefore performed a health risk assessment of occupational exposure to positive photoresists in a single optoelectronic semiconductor factory in Taiwan. Positive photoresists are widely used in the optoelectronic semiconductor industry for photolithography. Occupational exposure was estimated using the Stoffenmanager® model. Bayesian modeling incorporated available personal air sampling data. We examined the composition and by-products of the photoresists according to descriptions published in the literature and patents; the main compositions assessed were propylene glycol methyl ether acetate (PGMEA), novolac resin, photoactive compound, phenol, cresol, benzene, toluene, and xylene. Reference concentrations for each compound were reassessed and updated if necessary. Calculated hazard quotients were greater than 1 for benzene, phenol, xylene, and PGMEA, indicating that they have the potential for exposures that exceed reference levels. The information from our health risk assessment suggests that benzene and phenol have a higher level of risk than is currently acknowledged. Undertaking our form of risk assessment in the workplace design phase could identify compounds of major concern, allow for the early implementation of control measures and monitoring strategies, and thereby reduce the level of exposure to health risks that workers face throughout their career.

KEY WORDS: Bayesian modeling; photolithography; photoresist; risk assessment; Stoffenmanager®

1. INTRODUCTION

The semiconductor industry is a rapidly growing field, employing millions of workers worldwide and achieving global sales totaling over US$400 billion in 2017 (Rosso, 2018). The processes of manufacturing semiconductors involve various solvents, acids, and gases that have numerous toxic effects (Bailar et al., 2002; Hammond et al., 1995; LaDou & Rohm, 1998; Sorahan, Waterhouse, McKiernan, & Aston, 1985; Wald & Jones, 1987; Yoon, 2012). Although these processes are generally executed in a highly controlled manufacturing environment, concerns have long been expressed around the potential adverse health effects faced by workers (Kim, Kim, & Paek, 2014). Management and assessment of these hazardous chemical are complicated by the rapid pace of change in manufacturing processes and the necessity for trade secrecy in the industry (Smith & English, 2012; Smith, Sonnenfeld, & Pellow, 2007). Several epidemiologic assessments of adverse health effects associated with semiconductor production have reported higher rates of mortality and various cancers, including leukemia, non-Hodgkin lymphoma (Lee, Kim, Park, & Kang, 2011), tumors of the brain (Beall et al., 2005; Darnton et al., 2012),

Institute of Occupational Medicine and Industrial Hygiene, National Taiwan University, Taiwan.
*Address correspondence to Kuen-Yuh Wu, Institute of Occupational Medicine and Industrial Hygiene, National Taiwan University, R721, No. 17, Xu-Zhou Road, Zhongzheng District, Taipei, Taiwan, 10055; tel: +886 233668267; kuenyuhwu@ntu.edu.tw.

prostate (Beall et al., 2005), lung (McElvenny et al., 2003), pancreas (Nichols & Sorahan, 2005), and thyroid (Lee et al., 2011) among people working in the industry, compared with the general population. A recent review concluded that despite inconsistencies in reported excess risks between these studies and methodological limitations such as selection bias and misclassification, there are reasonable grounds to suspect that exposure to chemicals used in semiconductor production is associated with risks of reproductive abnormalities, cancers, and respiratory, dermal, and musculoskeletal disorders (Kim et al., 2014).

Of the many subprocesses involved in the fabrication of semiconductor chips, photolithography is of particular concern, with its high volume of various chemicals used at the processing stage (Chelton, Glowatz, & Mosovsky, 1991; Smith & English, 2012). The technique involves the application of photoresist, a light-sensitive material that undergoes photochemical reaction upon exposure to ultraviolet light onto a wafer. Circuit patterns are formed by selectively masking a specific area of the photoresist from exposure (Organisation for Economic Co-operation and Development [OECD], 2010; Smith & English, 2012). Several varieties of photoresists are often used in high quantities, with limited regulations (Chelton et al., 1991; Chepesiuk, 1999; Smith & English, 2012). Few toxicology studies exist concerning the potential health hazards of photoresists (Chelton et al., 1991; Integrated Laboratory Systems, 2006; OECD, 2010; Park et al., 2011; Smith & English, 2012), although epidemiologic studies assessing effects associated with use of the photolithography process have reported respiratory symptoms (McCurdy et al., 1995), skin rashes in females (Pastides, Calabrese, Hosmer, & Harris, 1988), and decreased white blood cell counts (Luo, Hsieh, Chang, & Hsu, 2002).

Recent literature indicates that several photoresist components may become volatile during operation, suggesting that they are not only sources of potential hazards but also materials that can be monitored for occupational exposure (Claussen, Lorenz, Penner, Vogt, & Sperlich, 2001; Integrated Laboratory Systems, 2006; Roy, Basu, Raghunathan, & Eswaran, 2003). We describe outcomes from a health risk assessment of exposure to positive photoresists, a commonly used type of photoresist (Yeh, Noga, Lawson, Tolbert, & Henderson, 2010), among photolithography workers in Taiwan.

2. METHODS

2.1. Hazard Identification of Photoresists

The positive photoresist assessed in this study is a commonly used type called the diazonaphthoquinone (DNQ)-Novolac photoresist, which uses propylene glycol monomethyl ether acetate (PGMEA) as the carrier solvent (Chelton et al., 1991; Integrated Laboratory Systems, 2006; OECD, 2010; Roy et al., 2003; Smith & English, 2012). Photoresists undergo photochemical reactions and decompose to low–molecular weight compounds, including phenol, cresol, benzene, toluene, xylene, and other benzene-based aromatic compounds, in addition to the carrier solvent (Park et al., 2011). Several adverse health effects are associated with these compounds. Preclinical investigations have documented central nervous system depression and hepatic changes following PGMEA exposure, which quickly hydrolyzes to PGME upon absorption (Domoradzki, Brzak, & Thornton, 2003; OECD, 2000, 2001; Spencer et al., 2002; U.S. Environmental Protection Agency [U.S. EPA], 1991). Phenol and cresol are known to target skin and mucosal membranes, in addition to their potential immunotoxic effects (Agency for Toxic Substances and Disease Registry [ATSDR], 2007a, 2008a, 2008b; Hoffman et al., 2001; Louei Monfared, Jaafari, & Sheibani, 2014; Sanders et al., 2009; U.S. EPA, 2002). Chronic benzene exposure is associated with hematotoxicity, including anemia and leukopenia, as well as leukemia (ATSDR, 2007a; Bayliss, Jinot, & Sonawane, 2002; Lan et al., 2004; U.S. EPA, 2003). Toluene and xylene are known to result in neurotoxicity (causing neurological impairment), with symptoms of impaired neuromuscular performance, hearing damage, and color vision deficits (ATSDR, 2007b; Flowers, 2005).

We undertook a literature review of toxicological studies to ensure that our assessment contained up-to-date threshold limit values. We reviewed assessments that applied a conservative estimate and the benchmark dose (BMD) method to derive quantitative limit values, yielding reference concentrations (RfCs), inhalation unit risks (IURs), and minimal risk levels (MRLs). No values are available in the literature for phenol or cresol because of a lack of well-documented evidence on the effect of chronic exposure by inhalation. For better comparison with other compounds, we calculated the RfCs of phenol and cresol, using the U.S. EPA's BMD method (Davis, Gift, & Zhao, 2011; U.S.

Table I. Summary of Limit Values Used for Each Compound

	Endpoint	RfC (mg/m^3)
PGMEA	Mild reversible sedation	2.0 (PGME) (IRIS, 1991)
Phenol	Irritation	1.93×10^{-3} (derived)
Cresol	Hyperplasia	1.26 (derived)
Xylene	Nervous system	1×10^{-1} (IRIS, 2003)
Toluene	Nervous system	5 (IRIS, 2005)
Benzene	Hematotoxicity	9.6×10^{-3} (ATSDR, 2007)

Note: RfC: reference concentration; PGMEA: propylene glycol methyl ether acetate; PGME: propylene glycol methyl ether.

EPA, 2012a, 2012b). We established a summary for each compound (Table I). Further details on the dose–response assessment and toxicological profile review are available in the Supporting Information.

2.2. The Exposure Scenario

We undertook chemical control banding at the photolithography station of an optoelectronics semiconductor fabrication factory in Taiwan to identify the material for assessment. Chemicals were ranked by the level of concern according to their hazard classifications, scale of use, and their volatility (International Labour Organization [ILO], 2006; Zalk & Nelson, 2008). The safety datasheet for the selected positive type of photoresist detailed its composition as being 50%–80% PGMEA, 10%–35% Novolac resins, and 0.1%–0.5% DNQ. A proportional composition of 65% for PGMEA and 35% for Novolac resin and DNQ combined was assumed. It was also assumed that all of the Novolac resin and DNQ would decompose into the identified byproducts, with their relative proportions based on the gas chromatography–mass spectroscopy peak area percentages from the simulation study conducted by Park et al. (2011) as follows: phenol, 5.33%; cresol, 21.8%; benzene, 2.19%; xylene, 3.76%; and toluene, 1.88%.

Onsite walkthrough surveys were conducted to collect information for the exposure scenario. At the assessed factory, the photolithography process took place in a room measuring ~300 m^2 in area with a height of 5.5 m, including an elevated floor level of 0.6 m for general ventilation circulation. The overall height also included a ceiling gap of 1.9 m to house ventilation outlets and pipes. Mechanical general ventilation was set to operate at around 30 air changes per hour (ACH). Multiple stations were in the room for each stage of the photolithography process, including the coating of photoresists, ultraviolet light exposure, developing, and etching. The processed wafers had a diameter of 0.06 m. The photoresists were first coated on top of the wafer at the spin coating station. Excess photoresists were removed by spinning the wafer at moderate speed. Following the coating process, each batch of wafers was taken out of the station by hand to be placed on a cart, which was transferred to the light exposure station for inducing the photochemical reaction. Wafers were automatically exposed one by one to ultraviolet light. Upon exposure, they were transferred to etching and developing, where the unwanted portion of photoresists was removed. The specific order and the number of coating layers required for each wafer depended on the product specification; those details were not available for this assessment. All stations were enclosed and equipped with local exhaust ventilation (LEV) systems. During operation, workers would stand close to the stations. They worked on eight-hour shift rotations and were required to wear protective clothing, PVC gloves, and activated carbon half-facemasks.

2.3. Exposure Assessment

Applying the quantitative exposure model was difficult in this study, because the specific details of the exposure scenario, such as the precise amount of photoresists used per wafer, coating time, light-exposed time, and LEV rates, were considered to be trade secrets. This lack of information increases the uncertainties in the estimation of exposure parameters, so we had to use a more conservative estimate of exposure. Furthermore, as photoresist models may be swapped frequently, a simpler model is needed for the efficient evaluation of a large variety of photoresists and their compositions to identify components of concern. Due to these considerations, this study favored mechanistic models based on the source–receptor approach. We selected Stoffenmanager® from the available mechanistic models, based on our review of past validations and sensitivity studies that compared common mechanistic tools. Overall, estimates by the Stoffenmanager approach yield more accurate estimates than those from the other models of the same tier and remain conservative when compared to higher tier models, which sometimes underestimate the exposure (Koppisch, Schinkel, Gabriel, Fransman, & Tielemans, 2012; Landberg, Axmon, Westberg, & Tinnerberg, 2017; Riedmann, Gasic, & Vernez, 2015; Schinkel et al., 2010; Spinazzè et al.,

2017). Navigation of Stoffenmanager quantitative exposure estimation module is briefly outlined in the Supporting Information.

2.3.1. *Stoffenmanager® 7.1*

We used Stoffenmanager® 7.1 (www.stoffenmanager.nl) to estimate workers' exposure; this first-tier quantitative inhalation exposure module is recognized by European legislation on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). Concentrations are estimated from a mixed-effect regression of occupational sampling databases with the Stoffenmanager score (C_t), which accepts semiqualitative measures as parameters; these measures include the vapor pressure of chemical used, the type of work performed, types of local control measures, the availability of general ventilation, and whether tasks are remotely operated (Marquart et al., 2008; Tielemans et al., 2008). Stoffenmanager outputs four percentiles (50th, 75th, 90th, and 95th) to characterize the variances around the geometric mean (Tielemans et al., 2008):

$$\hat{Y} = \exp\left[B_0 + B_1 \times \mathrm{Ln}(C_t)\right],$$

$$\hat{Y}_{percentiles} = \hat{Y} \times \exp\left[Z \times \sqrt{\sigma^2_{\mathrm{bc}} + \sigma^2_{\mathrm{wc}}}\right],$$

where $\hat{Y}$ is the estimated geometric mean of the exposure level, and ${\sigma^2}_{\mathrm{bc}}$ and ${\sigma^2}_{\mathrm{wc}}$ are the between- and within-company variances, respectively; B_0 and B_1 are the coefficients that vary depending on the physical properties of the chemical; and Z is the Z value for standard normal distribution.

However, there are drawbacks associated with the use of models such as Stoffenmanager, which was primarily designed as a screening tool. Its wider range of uncertainty as compared with that used by other higher tier models for the estimate ensures a protective, conservative prediction, but this level of conservatism may lead to overestimation of some scenarios, especially in those with lower exposure levels (Landberg et al., 2017). Moreover, while users find it is easier to obtain parameters for Stoffenmanager than for other models, the fact that the user is obliged to select suitable categories for each parameter potentially leads to reliability issues between different users (Landberg et al., 2015; Schinkel et al., 2014). In an effort to address concerns around reliability, we consulted onsite industrial hygienists for advice on the suitable selection of parameters.

2.3.2. *Bayesian Model Using Markov Chain Monte Carlo (MCMC)*

To improve the exposure estimates of Stoffenmanager, a Bayesian model is used to incorporate available measurement data. Stoffenmanager's estimates can be interpreted as a prior knowledge of the potential exposure distribution before actual measurement data are observed. The availability of personal sampling data for PGMEA enabled us to combine this information with Stoffenmanager's estimates in Bayesian modeling. Bayesian methods have previously been used to incorporate prior data or exposure modeling results to improve the interpretation of limited sampling data (Hewett, Logan, Mulhausen, Ramachandran, & Banerjee, 2006; Koppisch et al., 2012; Marquart et al., 2008; van de Ven et al., 2010). We used the method detailed by Quick, Huynh, & Ramachandran (2017) to specify prior distribution parameters based on Stoffenmanager's output, with the following distributions for the μ and σ^2 parameters:

$$\mu \sim \text{Truncated Normal}\left(\bar{y}_0, \frac{s^2_{y0}}{n_0}\right)\left[a_\mu, b_\mu\right],$$

$$\sigma^2 \sim \text{Truncated Inverse Gamma}\left(\frac{n_0 - 1}{2}, \frac{(n_0 - 1)\, s^2_{y0}}{2}\right)\left[a^2_\sigma, b^2_\sigma\right],$$

where $\bar{y}_0$, s^2_{y0}, and n_0 denote the mean, variance, and "sample size" of Stoffenmanager's predicted distribution, respectively. The "sample size" of the prior distribution represents the weight placed on the prior information relative to the sampling data, signifying the level of confidence given to the information. For this study, the sample size of the prior distribution was given a weight of $n = 3$, equivalent to the sample size of available data. The Bayesian priors were bounded to avoid unreasonable values due to small observations. Quick et al. (2017) recommend bounding priors based on thresholds of decision making. However, this study did not set the lower bounds, as they had almost no impact on the results. As for the upper bounds, the parameters were redistributed in such a way that the upper bound of the X_{95} posterior would be less than 50 times the RfC value, which should be a sufficiently large threshold above the actual exposure level. The Bayesian model was performed by the MCMC method using OpenBUGS software (http://www.openbugs.net). With a thinning

interval of 10 samples, a total of 15,000 samples was drawn for the MCMC analysis. MCMC convergence was assessed using the MCMCvis R package version 0.10 (Youngflesh, 2018).

2.3.3. Sensitivity Analysis

The impact of prior specification was also assessed. Two main sources of prior variations were considered: (1) the exposure estimate of Stoffenmanager and (2) the confidence assigned to the prior distribution (n_0). One potential variation in the prior specification could arise from between-user variations in assigning parameters for Stoffenmanager. Past reliability surveys have found that among parameters used in Stoffenmanager and similar models, the parameter "type of activity/handling" tends to be the most sensitive, yet it also tends to have larger user variations in selection (Landberg et al., 2015; Riedmann et al., 2015; Schinkel et al., 2014). We varied "handling type" by one order above and one order below the original setting, to characterize the impact of prior sensitivity according to Stoffenmanager reliability (Fig. 1). The plot for σ is not shown, as the distribution remained the same at these settings. The other source considered, n_0, was varied with different values to evaluate the impact of the prior confidence on the posterior result. As n_0 increases, the strength of the prior distribution increases, indicating a high confidence for the prior information, hence assigning more weight over the likelihood data. Despite the name, as a Stoffenmanager exposure prediction does not have a corresponding sample size, n_0 is instead an arbitrary parameter that characterizes the confidence of the prediction. Values 1.1, 2, 3, and 5 were chosen for n_0 to observe its impact on the posterior distribution (Figs. 2 and 3). These values were selected as n_0 is recommended to be less than the sample size actual measurement data available, or less than 5 when the sample size is large, so that the contribution of the data is not outweighed (Quick et al., 2017).

2.4. Risk Characterization

The cancer risk was calculated as Cancer Risk = $I_{\mathrm{Ih}} \times$ IUR, and the hazard quotient (HQ) was calculated as HQ = I_{Ih}/RfC, where I_{Ih} is the concentration distribution to which a worker may be exposed. Variability and uncertainty within the exposure model used are expressed in probability distributions by Stoffenmanger, whereas the Bayesian model further calculates the uncertainties of the parameter estimates, given the available data. Other uncertainties arising as a result of assumptions used in the assessments are discussed.

3. RESULTS AND DISCUSSION

3.1. Exposure Assessment of Photoresist

3.1.1. Stoffenmanager Parameters

We selected the parameters for Stoffenmanager based on the previously described exposure scenario. For the process activity category, we selected "Handling of liquids on small surfaces or incidental handling of liquids" as the performed task. The task duration was set at 480 minutes, with a frequency of four to five days a week. The task was not performed in the breathing zone. The selected working room volume was "over 1,000 m^3" and was equipped with mechanical general ventilation. The working area was cleaned daily; it was subjected to regular inspections and maintenance. We selected containment of the source with LEV for control measures at source. The resulting Stoffenmanager estimation is shown in Table V.

3.1.2. Bayesian Model

PGMEA was the only chemical that was monitored regularly. Recorded personal sampling data of three workers from a full-day work shift were 2.05, 3.73, and 1.14 mg/m^3, respectively. The convergence of MCMC and identifiability of the Bayesian model were evaluated by visual inspection and calculation of the Gelman–Rubin statistic, and the percentage of the prior–posterior overlap. Trace and density plots are available in the Supporting Information. The posterior estimate of the concentration yielded a median of 1.68 (95% credible interval = [0.57, 3.34]) mg/m^3, with a 95th percentile of 4.93 (2.49, 21.78) mg/m^3 (Table II).

The prior–posterior overlaps suggest that the posterior distributions of μ and σ were all updated by the likelihood function, suggesting that the prior weight did not overpower the observed data (Tables III and IV). When compared to the estimated distribution provided by Stoffenmanager, the exposure distribution with updated posterior parameters shifted upward, as the recorded personal sampling data were all greater than the geometric mean of the Stoffenmanager estimate (Fig. 4).

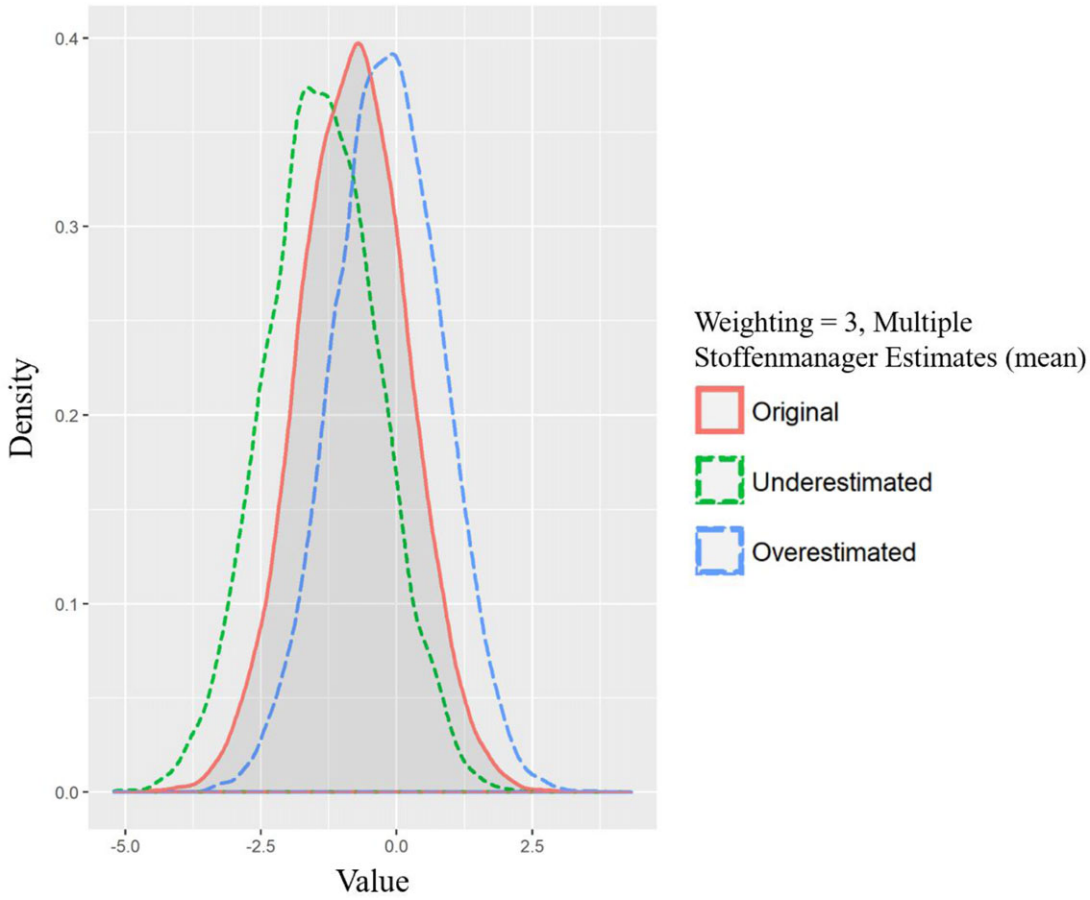

Fig. 1. Priors derived from varying the "handling type" parameters of Stoffenmanager.

Using the posterior medians of the parameters, the Bayesian model resulted in a narrower probability distribution closer to the mean of the sampling data (Fig. 4). As the available sample size provided limited data, uncertainties surround each parameter, which are expressed in the Bayesian model as distributions (Fig. 5). A more conservative estimate of the exposure using the 95th percentile value of each parameter yields an extremely high concentration (21.78 mg/m^3). In addition to the threshold of 50 times the RfC, thresholds of 100 and 200 were also tested to ensure that the restriction does not dramatically alter the posterior distribution. When the higher thresholds were used, higher extreme values were recorded, making visual inspection of convergence more difficult. However, the resulting statistics for the posterior mean, median, and the 95% credible interval remained almost unchanged, indicating that the bounding threshold had little impact.

3.1.3. Sensitivity Analysis

The sensitivity analysis results summarized in Fig. 6 suggest that n_0 in general has a higher influence on the resulting posterior estimate. Furthermore, decreases in n_0 are mainly reflected in widened credible intervals for each parameter. In other words, when less confidence is specified in the prior distribution, the resulting posterior distribution is characterized by a higher chance of overestimating the exposure. In comparison, changes in Stoffenmanager estimation as a result of "handling type" parameter have a much smaller impact on the overall estimation, especially within the 50% credible interval, suggesting that the model is more robust to potential misspecifications in Stoffenmanager. While a lower n_0 would favor data over the prior distribution, for $n_0 = 1.1$ and $n_0 = 2$ the resulting prior–posterior overlap percentages increase accordingly (Tables III and IV), suggesting that the measurement data alone do not provide sufficient information to update the

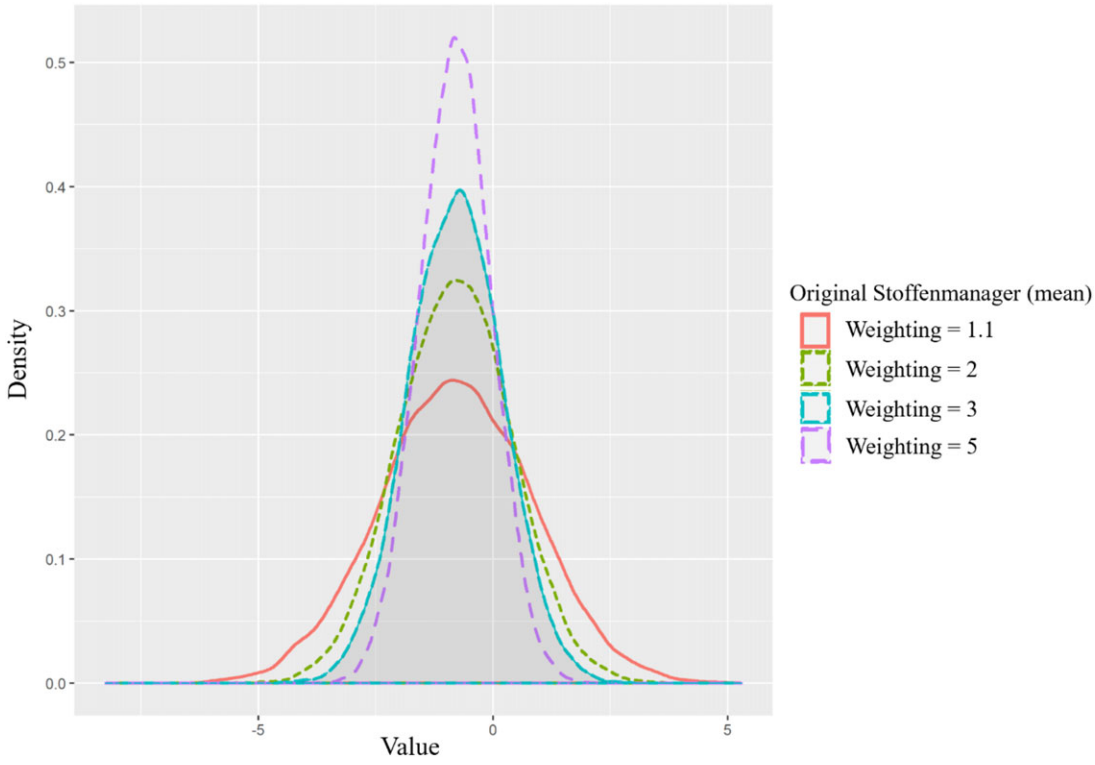

Fig. 2. Prior for μ at different weighting n_0 values.

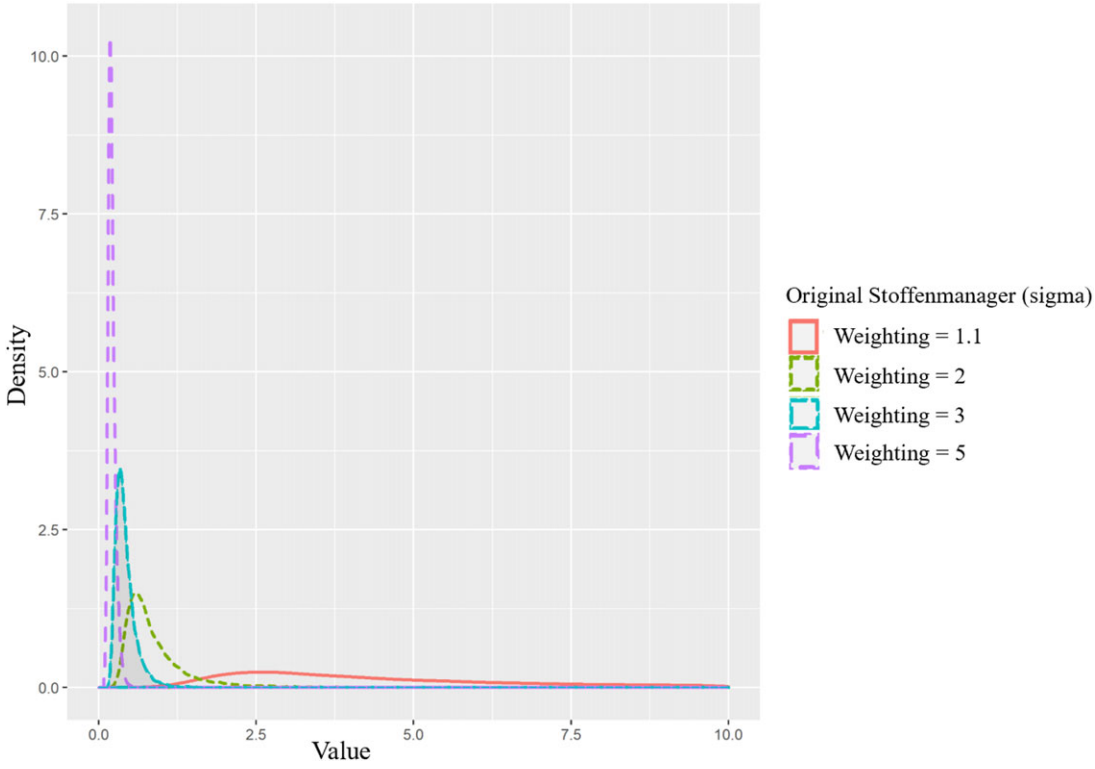

Fig. 3. Prior for σ at different weighting n_0 values.

Table II. Summary Statistics of Posterior Estimates

	Mean (*SD*)	Median (95% CI)
μ	0.47 (0.44)	0.52 [−0.56, 1.21]
σ	0.74 (0.34)	0.65 [0.356, 1.67]
GM	1.75 (0.70)	1.68 [0.57, 3.34]
GSD	2.27 (1.30)	1.92 [1.43, 5.31]
X_{95}	6.56 (5.93)	4.93 [2.49, 21.78]

Note: SD: standard deviation; CI: credible interval; μ: mean; σ: standard deviation; GM: geometric mean; GSD: geometric standard deviation; X_{95}: 95th percentile of the posterior estimate.

Table III. Prior–Posterior Overlap Percentages of μ Under Different Scenarios

Stoffenmanager	1.1	2	3	5
Underestimate	67.0	39.0	33.7	31.4
Original	71.3	30.0	18.8[a]	8.8
Overestimate	67.8	26.6	15.3	5.2

[a]Original calculation.

Table IV. Prior–Posterior Overlap Percentage of σ Under Different Scenarios

Stoffenmanager	1.1	2	3	5
Underestimate	34.3	36.6	34.7	25.3
Original	16.0	14.9	10.8[a]	6.5
Overestimate	9.6	5.9	3.2	1.1

[a]Original calculation.

prior distribution due to the limited sample size. On the other hand, a higher value of n_0 results in estimates with much smaller credible intervals, which was especially apparent for the 95th percentile exposure estimate. While this would result in a lower uncertainty, it also results in a higher risk of potentially underestimating the exposure level as a result of being overconfident about the prior specification. The exposure assessment could be improved by incorporating a greater volume of personal air sampling data, which would reduce the uncertainty due to the selection of n_0. However, when additional data collection is not possible, n_0 should be kept as small as possible, to avoid an overconfident posterior estimate. It is important to be cautious about the selection and specification of the model's parameters. The analysis suggests that the current assessment with $n_0 = 3$ is a reasonable and conservative default given the data available, as smaller values would cause wider variabilities in the exposure estimate due to insufficient information, while higher values could pose a higher risk of underestimating the exposure when such confidence is not warranted.

3.2. Risk Characterization

The resulting HQs and their 95th percentiles are shown in Table V.

The available PGMEA sampling data revealed that the exposure assessment reflected the actual exposure scenario. The use of the Bayesian model also allowed the measurement data to be incorporated, further increasing the confidence of the estimation. In contrast, the HQs of the other compounds were derived from the exposure estimations by Stoffenmanager. While more sampling data are needed to provide validation, HQs exceeding 1 suggest that further evaluations are warranted to assess the potential health risks of PGMEA, benzene, phenol, and xylene. Lower HQs for cresol and toluene suggest lower levels of health concerns for these compounds, especially when compared to phenol and benzene, which have higher HQs and cancer risks that indicate a prioritization of validation assessment in the event of limited resources.

The calculated HQs do not characterize the severity of the defined endpoints for each compound. When considering the severity of the endpoints, the RfCs for PGMEA and phenol are based on relatively mild effects. The reported symptoms of exposure to these compounds also tend to be reversible and associated with temporary effects at lower concentrations. For instance, in humans, the primary effects of PGME exposure mainly consist of irritation in the eyes, nose, and throat (U.S. EPA, 1991). In particular, while phenol has a larger HQ, its known corrosive irritant nature results in a sensitive endpoint (ATSDR, 2008b; U.S. EPA, 2002). For cresol, while studies have shown kidney and thyroid gland toxicity under chronic exposure, the RfC calculation is based on respiratory epithelium hyperplasia, a much milder endpoint (ATSDR, 2008a).

In contrast, numerous reports exist on the effects of exposure to xylene and toluene in the human nervous system. Benzene-related hematotoxicity is an early indicator of much more serious symptoms that have been reported in epidemiologic studies (Ahmad Khan, 2007; Bayliss et al., 2002; Lan et al., 2004; U.S. EPA, 2003). The major toxicity of concern with toluene is its effect on the central nervous system producing neurological impairment, with symptoms including fatigue, headache, impairment of cognitive

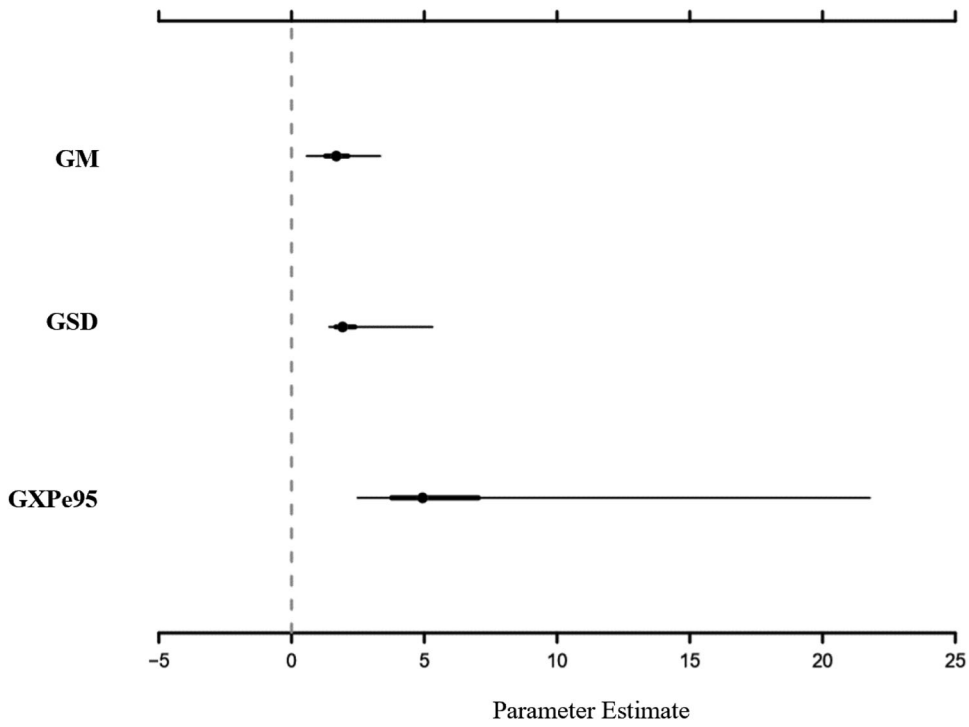

Fig. 4. Posterior parameter estimates for the geometric mean (GM), geometric standard deviation (GSD), and 95th percentile value (GXPe95). Center points represent the median, while the thicker and thinner intervals represent the 50% and 95% credible intervals, respectively.

and neuromuscular performance, hearing damage, and deficits in color vision (Flowers, 2005). Chronic xylene exposure is associated with neurologic effects such as headache, dizziness, and anxiety; an inability to concentrate; impaired learning; and a decrease in motor performance (ATSDR, 2007b). Finally, benzene is a known human carcinogen with all routes of exposure. The major effect of long-term exposure is an arrested development of blood cells, leading to hematotoxicity including cytopenia, anemia, and leukopenia, as well as leukemia (ATSDR, 2007a; Bayliss, Chen, Jarabek, Sonawane, & Valcovic, 1998; Rothman et al., 1996; U.S. EPA, 2003). Thus, compounds with more severe endpoints and higher HQs that should be prioritized for action include benzene, xylene, and phenol.

3.3. Potential Application in a Risk-Informed Design Process for a Workplace Prior to Operation

As benzene is a highly regulated compound because of its known toxicity, products that contain a significant amount of benzene are often required to meet certain labeling requirements (ATSDR, 2007a). The HQ and cancer risk of benzene are both sensitive to the assigned composition percentage of the photoresist (Table VI), suggesting that the health risk of benzene is of potential concern, even at the composition percentage of 10^{-2}. The high cancer risk and HQ presented in this study should be viewed as an indicator of potential risk that calls for prioritized further validation.

Photolithography is a crucial procedure in the fabrication process, in terms of engineering and production. Numerous studies have investigated the design and optimization of photolithography from the engineering perspective, including the use of tools such as simulation models and integrated definition (IDEF0) methods characterizing each task involved in the process (Arisha, Young, & El Baradie, 2004; Doniavi, Mileham, & Newnes, 2000; Yang, 2006). Changes in parameters such as the baking time, amount of photoresist coating, and flow rate necessary for optimizing production performance mean that the resulting exposure scenario may have a competing outcome for occupational health. For instance, a stronger LEV flow rate lowers the photoresist spin coating quality, yet the absence of the LEV may pose a significant health risk to operators

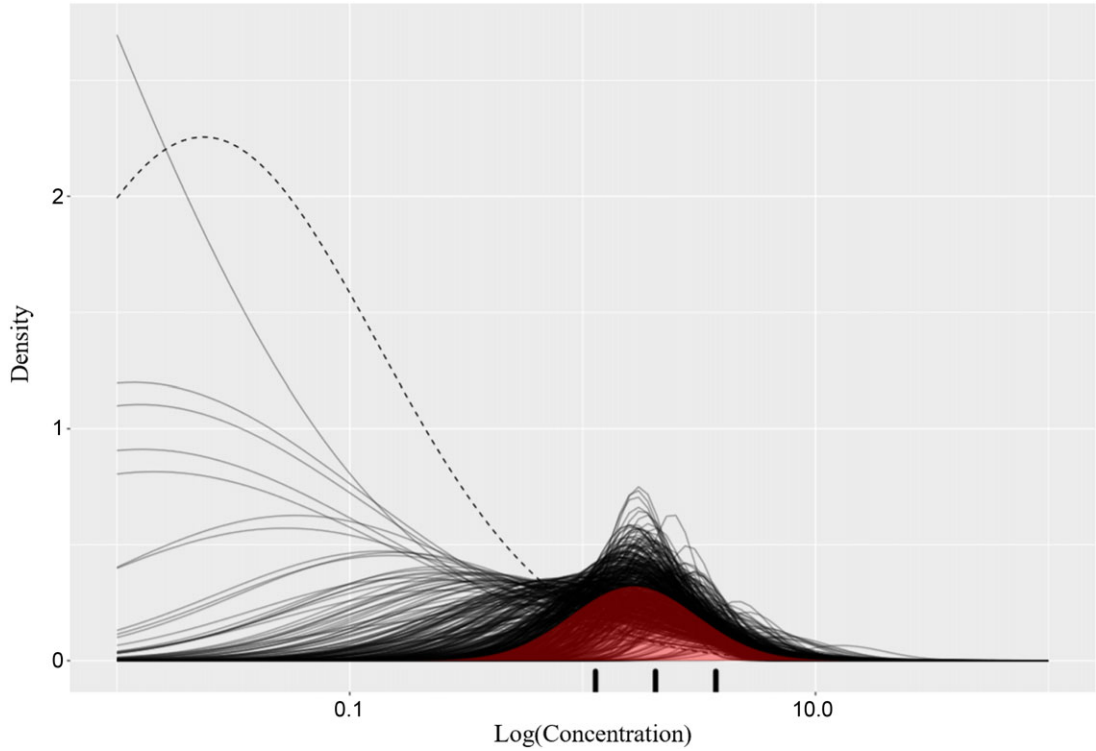

Fig. 5. Comparison of the posterior distributions of the Bayesian model with the Stoffenmanager estimate (dotted line). The figure shows the resulting exposure distribution based on the parameters drawn from 500 sampled iterations of the MCMC chains. The shaded density shows the distribution based on the medians of the parameters. The rug plot on the *x*-axis shows the three recorded data used in the Bayesian model. MCMC: Markov Chain Monte Carlo.

(Arisha et al., 2004). Performing a health risk assessment based on the workplace design characterizes risk and adds health risk outcomes that ensure full optimization of the process, facilitating communication between process engineers and industrial hygienists at the design and optimization stages.

Mechanistic exposure models such as Stoffenmanager provide useful insights for the selection of appropriate control measures for future workplace designs. This evaluation of how different proportions of benzene in photoresists may affect the resulting cancer risk enables the use of risk characterization for selecting suitable materials, composition, and the appropriate measures of control. Information such as the layout of a factory, tasks performed, materials used, and control measures are all readily available parameters in the design phase, so this method can potentially be extended to assess factory designs by first estimating the daily exposure level based on the workplace design, then characterizing the risks associated with the scenario.

While the application of risk assessment in the design phase has been proposed and emphasized, the majority of the literature focuses on performing a safety assessment (Creaser, 2008; Health and Safety Executive, 2015; Safe Work Australia, 2014). For a health risk assessment, a suitable tool should be able to estimate the average daily exposure level based on the process, workplace design, and operating conditions (Hassim, 2016; Hassim & Edwards, 2006). The assessment presented in this study highlights potential opportunities and challenges for this application.

3.4. Uncertainties Involved in This Assessment

The reliability of Stoffenmanager has been discussed in prior studies (Landberg et al., 2015; Marquart et al., 2008; Schinkel et al., 2014). As mechanistic exposure models require users to categorize model parameters based on personal judgment, uncertainty may arise. A recent study has shown that when inputting an exposure scenario to the Stoffenmanager web-based tool, between-user variances can be large, especially for the following parameters: handling type, breathing zone, personal protection, and control measures, due to difficulties in

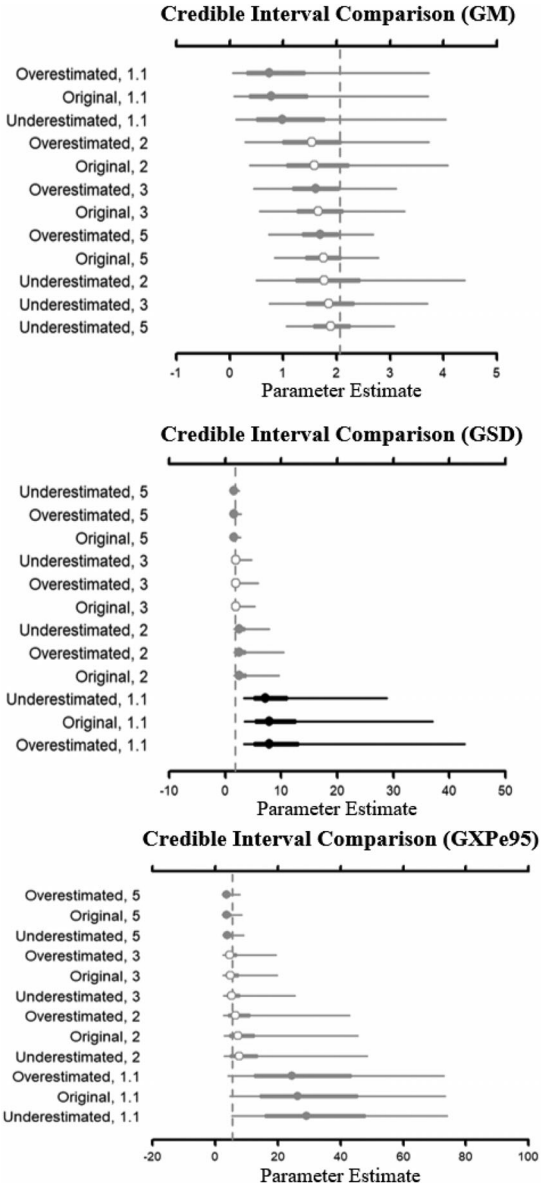

Fig. 6. Parameter estimates of the geomteric mean (GM), geometric standard deviation (GSD), and 95th percentile (GXPe95) under different scenarios.

Note: Each scenario labeled by the Stoffenmanager estimate used and the weight assigned for prior distribution (n = 1.1, 2, 3, or 5); Overestimated: Stoffenmanager estimate with overestimated task handling; Original: Stoffenmanager estimate with original task handling; Underestimated: Stoffenmanager estimate with underestimated task handling. Vertical dotted lines represent corresponding parameters of the actual personal air sampling data for reference. Thick and thin lines represent 50% and 95% credible intervals (CIs), respectively. Gray lines indicate that the 95% CI of parameters overlaps with the vertical reference. Points represent posterior medians, in which open circles indicate that the 50% CI overlaps with the vertical reference, while closed circles indicate otherwise.

interpretation and categorization (Landberg et al., 2015). Our study findings were similar to those of Schinkel et al. (2014) in regard to the reliability of the Advanced REACH Tool (ART), a higher tiered model that is based on the same source receptor approach (Schinkel et al., 2014). The descriptions of the activity parameter in Stoffenmanager made use of general analogies to common industry tasks to increase applicability in a variety of industries (Marquart et al., 2008). However, such analogies may be more subject to personal judgment when applied to the semiconductor industry, where tasks performed are likely to deviate from traditional activities. An exposure model with industry-specific modifications would potentially increase the reliability of the tool.

Our results showed that benzene posed an especially high cancer risk and an HQ exceeding 1, indicating an unacceptable level of risk. However, the estimation was based on the assumption that benzene assumed a likely overestimated proportion, that is, 2.19% of the photoresist composition after a photochemical reaction. In a recent risk assessment conducted by Torres et al. (2014), benzene was not identified as a process chemical. Their decision has been criticized (Paek & Gassert, 2015), as previous reports have detailed the presence of benzene in the fabrication process (Jones et al., 2015; Paek & Gassert, 2015; Torres et al., 2014). Similarly, the exposure scenario we have assessed did not monitor benzene in the photolithography process as it was not identified as a process chemical. However, based on our results, we recommend collection of benzene personal air sampling data to reduce the uncertainties involved.

We conducted dose–response assessments for phenol and cresol, as no RfCs were available in the literature. This lack of information necessitated a higher uncertainty factor in the calculation of the RfCs for these compounds. Integrated Risk Information System (IRIS) has not yet provided an official RfC for phenol, while the U.S. EPA has provided a provisional RfC of 0.006 mg/m^3 (U.S. EPA, 1998), suggesting that EPA peer reviews have failed to reach a consensus. For the other compounds, the uncertainties relating to the RfCs relate to the quality of the critical toxicity studies providing the evidence basis for the calculations. For instance, benzene and toluene have more in-human studies reporting observed dose–responses, whereas the other RfCs are based on animal studies, resulting in higher uncertainties due to potential interspecies variances.

Table V. Concentration Distributions of Each Compound Estimated by Stoffenmanager and Their Corresponding Hazard Quotients (HQ)

	Stoffenmanager Estimates (mg/m^3)				Bayesian Model	HQ
	50th	75th	90th	95th	GM (X_{95})	GM [95%CI](X_{95} [95% CI])
PGMEA	0.45	1.43	4.05	7.59	1.68 (4.93)	0.84 [0.29, 1.67](2.47 [1.25, 10.89])
Benzene	0.36	1.15	3.27	6.12	–	37.5 (637.5)
Phenol	0.0085	0.027	0.076	0.14	–	4.40 (72.54)
Cresol	0.065	0.21	0.59	1.11	–	0.052 (0.88)
Xylene	0.15	0.47	1.33	2.49	–	1.5 (24.9)
Toluene	0.17	0.56	1.57	2.94	–	0.034 (0.59)

Note: PGMEA: propylene glycol methyl ether acetate; 50th: 50th percentile; 75th: 75th percentile; 90th: 90th percentile; 95th: 95th percentile; GM: geometric mean of posterior estimate; X_{95}: 95th percentile of the posterior estimate; CI: credible interval.

Table VI. Estimated HQs and Cancer Risks of Benzene in Photoresists at Different Composition Percentages

	HQ		Cancer Risk	
Benzene%	GM	X_{95}	$GM_{lower, upper}$	$X_{95lower, upper}$
5%	8.75E+01	1.48E+03	[1.86E-03, 3.16E-02]	[6.55E-03, 1.11E-01]
4%	7.81E+01	1.32E+03	[1.67E-03, 2.81E-02]	[5.85E-03, 9.87E-02]
3%	6.67E+01	1.13E+03	[1.42E-03, 2.41E-02]	[4.99E-03, 8.47E-02]
2%	5.42E+01	9.13E+02	[1.15E-03, 1.94E-02]	[4.06E-03, 6.83E-02]
1%	3.75E+01	6.31E+02	[7.99E-04, 1.35E-02]	[2.81E-03, 4.73E-02]
0.5%	2.60E+01	4.38E+02	[5.55E-04, 9.32E-03]	[1.95E-03, 3.28E-02]
0.1%	1.15E+01	1.86E+02	[2.44E-04, 3.97E-03]	[8.58E-04, 1.40E-02]
0.01%	3.23E+00	5.52E+01	[6.88E-05, 1.18E-03]	[2.42E-04, 4.13E-03]

Note: HQ: hazard quotient; GM: geometric mean; X_{95}: 95th percentile of the posterior estimate.

The precise composition and by-products of the photoresist may not be consistent, as they can vary according to the specification of the manufactured products. The DNQ-Novolac type of the positive photoresist assessed in this study uses PMGEA as the main carrier solvent, which may be viewed as a generic version of positive photoresists that are commonly used today (Integrated Laboratory Park et al., 2011; Roy et al., 2003; Systems, 2006). Furthermore, other common photoresists, such as those used in deep ultraviolet photolithography, replace the photoactive compound component with photoacid generators, which reportedly induce outgassing of vapors such as benzene upon exposure to ultraviolet light.

4. CONCLUSION

The results of the conducted health risk assessment of chronic exposure to by-products of positive photoresists used in the photolithography process suggest that benzene, PGMEA, xylene, and phenol had HQs exceeding 1. Benzene and phenol were associated with the greatest level of risk, suggesting that resources should be prioritized to validate and reduce the uncertainties of the assessment by collecting more air sampling data. This study also demonstrated the use of Stoffenmanager as a source for specifying prior distribution in a Bayesian model to incorporate personal air sampling data for PGMEA, reducing the uncertainties of the assessment, especially when compared to exposure assessment conducted with either method alone, which would have been limited by the low sample size and possible overconservatism for personal air sampling and Stoffenmanager, respectively. As prior data are often available for various exposure scenarios, the use of Bayesian modeling allows this information to be applied and integrated into a risk assessment, while enabling an iterative assessment process when new data become available. Furthermore, as information used in this assessment can be obtained even before a workplace is in operation, the risk assessment conducted in this study can potentially be carried out early in the design stage and thus identify potential risks that should be anticipated and addressed. When informed in this way, design decisions can

incorporate relevant risk reduction measures early in the lifecycle of a workplace, at a timepoint when modifications can often be made more effectively, improving protection measures for the workers' health.

ACKNOWLEDGMENTS

The use of Stoffenmanager® was performed in cooperation with and with permission of Cosanta BV. The authors would also like to thank Iona MacDonald for the constructive feedback of the article.

REFERENCES

Agency for Toxic Substances and Disease Registry (ATSDR). (2007a). *Toxicological profile for benzene*. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.

Agency for Toxic Substances and Disease Registry (ATSDR). (2007b). *Toxicological profile for xylenes*. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.

Agency for Toxic Substances and Disease Registry (ATSDR). (2008a). *Toxicological profile for cresols*. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.

Agency for Toxic Substances and Disease Registry (ATSDR). (2008b). *Toxicological profile for phenol*. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.

Ahmad Khan, H. (2007). Benzene's toxicity: A consolidated short review of human and animal studies. *Human and Experimental Toxicology*, *26*(9), 677–685. https://doi.org/10.1177/0960327107083974.

Arisha, A., Young, P., & El Baradie, M. (2004). A simulation model to characterize the photolithography process of a semiconductor wafer fabrication. *Journal of Materials Processing Technology*, *155–156*, 2071–2079. https://doi.org/10.1016/J.JMATPROTEC.2004.04.387.

Bailar, J. C., Greenberg, M., Harrison, R., LaDou, J., Richter, E., & Watterson, A. (2002). Cancer risk in the semiconductor industry: A call for action. *International Journal of Occupational and Environmental Health*, *8*(2), 163–168.

Bayliss, D., Jinot, J., & Sonawane, B. (2002). *Toxicological review of benzene (noncancer effects) (CAS No. 71-43-2) in support of summary information on the integrated risk information system (IRIS) (EPA/635/R-02/001F)*. Washington, DC: U.S. Environmental Protection Agency.

Bayliss, D. L., Chen, C., Jarabek, A., Sonawane, B., & Valcovic, L. (1998). *Carcinogenic effects of benzene: An update (draft report) (EPA/600/P-97/001F)*. Washington, DC: U.S. Environmental Protection Agency.

Beall, C., Bender, T. J., Cheng, H., Herrick, R., Kahn, A., Matthews, R., … Delzell, E. (2005). Mortality among semiconductor and storage device-manufacturing workers. *Journal of Occupational and Environmental Medicine*, *47*(10), 996–1014.

Chelton, C. F., Glowatz, M., & Mosovsky, J. A. (1991). Chemical hazards in the semiconductor industry. *IEEE Transactions on Educations*, *34*(3), 269–288.

Chepesiuk, R. (1999). Where the chips fall: Environmental health in the semiconductor industry. *Environmental Health Perspectives*, *107*(9), A452–A457.

Claussen, W., Lorenz, B., Penner, K., Vogt, M., & Sperlich, H.-P. (2001). United States Patent No. US 6245640 B1. United States Patent.

Creaser, W. (2008). Prevention through design (PtD): Safe design from an Australian perspective. *Journal of Safety Research*, *39*(2), 131–134. https://doi.org/10.1016/j.jsr.2008.02.018.

Darnton, A., Miller, B. G., Maccalman, L., Galea, K. S., Wilkinson, S., Cherrie, J. W., … Osman, J. (2012). An updated investigation of cancer incidence and mortality at a Scottish semiconductor manufacturing facility with case-control and case-only studies of selected cancers. *Occupational and Environmental Medicine*, *69*(10), 767–769. https://doi.org/10.1136/oemed-2011-100606.

Davis, J. A., Gift, J. S., & Zhao, Q. J. (2011). Introduction to benchmark dose methods and U.S. EPA's benchmark dose software (BMDS) version 2.1.1. *Toxicology and Applied Pharmacology*, *254*(2), 181–191. https://doi.org/10.1016/J.TAAP.2010.10.016.

Domoradzki, J. Y., Brzak, K. A., & Thornton, C. M. (2003). Hydrolysis kinetics of propylene glycol monomethyl ether acetate in rats in vivo and in rat and human tissues in vitro. *Toxicological Sciences*, *75*(1), 31–39. https://doi.org/10.1093/toxsci/kfg177.

Doniavi, A., Mileham, A. R., & Newnes, L. B. (2000). A systems approach to photolithography process optimization in an electronics manufacturing environment. *International Journal of Production Research*, *38*(11), 2515–2528. https://doi.org/10.1080/00207540050031896.

Flowers, L. (2005). *Toxicological review of toluene (CAS No. 108-88-3) in support of summary information on the integrated risk information system (IRIS) (EPA/635/R-05/004)*. Washington, DC: U.S. Environmental Protection Agency.

Hammond, S. K., Hammond, S. K., Hines, C. J., Hallock, M. F., Woskle, S. R., Abdollahzadeh, S., … Schenker, M. B. (1995). Tiered exposure-assessment strategy in the semiconductor health study. *American Journal of Industrial Medicine*, *28*(6), 661–680. https://doi.org/10.1002/ajim.4700280604.

Hassim, M. H. (2016). Comparison of methods for assessing occupational health hazards in chemical process development and design phases. *Current Opinion in Chemical Engineering*, *14*, 137–149. https://doi.org/10.1016/j.coche.2016.10.001.

Hassim, M. H., & Edwards, D. W. (2006). Development of a methodology for assessing inherent occupational health hazards. *Process Safety and Environmental Protection*, *84*(5), 378–390. https://doi.org/10.1205/psep.04412.

Health and Safety Executive. (2015). Managing health and safety in construction (design and management) regulations 2015. *Guidance on regulations*. London: HMSO.

Hewett, P., Logan, P., Mulhausen, J., Ramachandran, G., & Banerjee, S. (2006). Rating exposure control using Bayesian decision analysis. *Journal of Occupational and Environmental Hygiene*, *3*(10), 568–581. https://doi.org/10.1080/15459620600914641.

Hoffman, G. M., Dunn, B. J., Morris, C. R., Butala, J. H., Dimond, S. S., Gingell, R., & Waechter, J. M. (2001). Two-week (ten-day) inhalation toxicity and two-week recovery study of phenol vapor in the rat. *International Journal of Toxicology*, *20*(1), 45–52. https://doi.org/10.1080/109158101750103413.

Integrated Laboratory System. (2006). *Chemical information review document for diazonaphthoquinone derivatives used in photoresists. Supporting nomination for toxicological evaluation by the national toxicology program*. Research Triangle Park, NC: National Toxicology Program. U.S Department of Health and Human Services.

International Labour Organization (ILO). (2006). International chemical control toolkit draft guidelines. Retrieved from https://www.ilo.org/.

Jones, R. M., Dell, L., Torres, C., Simmons, C. E., Poole, J., Boelter, F. W., & Harper, P. (2015). Exposure reconstruction and risk analysis for six semiconductor workers

with lymphohematopoietic cancers. *Journal of Occupational and Environmental Medicine*, *57*(6), 649–658. https://doi.org/10.1097/JOM.0000000000000413.

Kim, M.-H., Kim, H., & Paek, D. (2014). The health impacts of semiconductor production: An epidemiologic review. *International Journal of Occupational and Environmental Health*, *20*(2), 95–114. https://doi.org/10.1179/2049396713Y.0000000050.

Koppisch, D., Schinkel, J., Gabriel, S., Fransman, W., & Tielemans, E. (2012). Use of the MEGA exposure database for the validation of the Stoffenmanager model. *Annals of Occupational Hygiene*, *56*(4), 426–439. https://doi.org/10.1093/annhyg/mer097.

LaDou, J., & Rohm, T. (1998). The international electronics industry. *International Journal of Occupational and Environmental Health*, *4*(1), 1–18. https://doi.org/10.1179/oeh.1998.4.1.1.

Lan, Q., Zhang, L., Li, G., Vermeulen, R., Weinberg, R. S., Dosemeci, M., … Smith, M. T. (2004). Hematotoxicity in workers exposed to low levels of benzene. *Science*, *306*(5702), 1774–1776. https://doi.org/10.1126/science.1102443.

Landberg, H. E., Axmon, A., Westberg, H., & Tinnerberg, H. (2017). A study of the validity of two exposure assessment tools: Stoffenmanager and the advanced REACH tool. *Annals of Work Exposures and Health*, *61*(5), 575–588. https://doi.org/10.1093/annweh/wxx008.

Landberg, H. E., Berg, P., Andersson, L., Bergendorf, U., Karlsson, J. E., Westberg, H., & Tinnerberg, H. (2015). Comparison and evaluation of multiple users' usage of the exposure and risk tool: Stoffenmanager 5.1. *Annals of Occupational Hygiene*, *59*(7), 821–835. https://doi.org/10.1093/annhyg/mev027.

Lee, H.-E., Kim, E.-A., Park, J., & Kang, S.-K. (2011). Cancer mortality and incidence in Korean semiconductor workers. *Safety and Health at Work*, *2*(2), 135–147. https://doi.org/10.5491/SHAW.2011.2.2.135.

Louei Monfared, A., Jaafari, A., & Sheibani, M. T. (2014). Histological and histometrical evidences for phenol immunotoxicity in mice. *Comparative Clinical Pathology*, *23*, 529–534. https://doi.org/10.1007/s00580-012-1645-9.

Luo, J., Hsieh, L., Chang, M., & Hsu, K. (2002). Decreased white blood cell counts in semiconductor manufacturing workers in Taiwan. *Occupational and Environmental Medicine*, *59*(1), 44–48. https://doi.org/10.1136/oem.59.1.44.

Marquart, H., Heussen, H., Le Feber, M., Noy, D., Tielemans, E., Schinkel, J., … Van Der Schaaf, D. (2008). "Stoffenmanager," a web-based control banding tool using an exposure process model. *Annals of Occupational Hygiene*, *52*(6), 429–441. https://doi.org/10.1093/annhyg/men032.

McCurdy, S. a., Pocekay, D., Hammond, S. K., Woskie, S. R., Samuels, S. J., & Schenker, M. B. (1995). A cross-sectional survey of respiratory and general health outcomes among semiconductor industry workers. *American Journal of Industrial Medicine*, *28*(6), 847–860.

McElvenny, D. M., Darnton, A. J., Hodgson, J. T., Clarke, S. D., Elliott, R. C., & Osman, J. (2003). Investigation of cancer incidence and mortality at a Scottish semiconductor manufacturing facility. *Occupational Medicine*, *53*(7), 419–430.

Nichols, L., & Sorahan, T. (2005). Cancer incidence and cancer mortality in a cohort of UK semiconductor workers, 1970–2002. *Occupational Medicine*, *55*(8), 625–630. https://doi.org/10.1093/occmed/kqi156.

Organisation for Economic Co-operation and Development (OECD). (2000). SIDS initial assessment report. 1-methoxy-2-propanol acetate (CAS No. 108-65-6).

Organisation for Economic Co-operation and Development (OECD). (2001). SIDS initial assessment report for 11th SIAM. 1-methoxypropan-2-ol (CAS No. 107-98-2).

Organisation for Economic Co-operation and Development (OECD). (2010). Emission scenario document on photoresist use in semiconductor manufacturing. Health and Safety Publications Series on Emission Scenario Documents.

Paek, D., & Gassert, T. H. (2015). Fatally flawed: Samsung's environ consultants. *Journal of Occupational and Environmental Medicine*, *57*(11), e141–e143. https://doi.org/10.1097/JOM.0000000000000575.

Park, S. H., Shin, J. A., Park, H. H., Yi, G. Y., Chung, K. J., Park, H. D., … Lee, I. S. (2011). Exposure to volatile organic compounds and possibility of exposure to by-product volatile organic compounds in photolithography processes in semiconductor manufacturing factories. *Safety and Health at Work*, *2*(3), 210–217. https://doi.org/10.5491/SHAW.2011.2.3.210.

Pastides, H., Calabrese, E. J., Hosmer, D. W., Jr., & Harris, D. R., Jr. (1988). Spontaneous abortion and general illness symptoms among semiconductor manufacturers. *Journal of Occupational Medicine*, *30*(7), 543–551.

Quick, H., Huynh, T., & Ramachandran, G. (2017). A method for constructing informative priors for Bayesian modeling of occupational hygiene data. *The Annals of Occupational Hygiene*, *61*(1), 67–75. https://doi.org/10.1093/annweh/wxw001.

Riedmann, R. A., Gasic, B., & Vernez, D. (2015). Sensitivity analysis, dominant factors, and robustness of the ECETOC TRA v3, Stoffenmanager 4.5, and ART 1.5 occupational exposure models. *Risk Analysis*, *35*(2), 211–225. https://doi.org/10.1111/risa.12286.

Rosso, D. (2018). Annual semiconductor sales increase 21.6 percent, top $400 billion for first time. Retrieved from https://www.semiconductors.org/annual-semiconductor-sales-increase-21-6-percent-top-400-billion-for-first-time/.

Rothman, N., Li, G.-L., Dosemeci, M., Bechtold, W. E., Marti, G. E., Wang, Y.-Z., … Hayes, R. B. (1996). Hematotoxocity among Chinese workers heavily exposed to benzene. *American Journal of Industrial Medicine*, *29*(3), 236–246.

Roy, D., Basu, P. K., Raghunathan, P., & Eswaran, S. V. (2003). DNQ-novolac photoresists revisited: 1H and13C NMR evidence for a novel photoreaction mechanism. *Magnetic Resonance in Chemistry*, *41*(2), 84–90. https://doi.org/10.1002/mrc.1134.

Safe Work Australia. (2014). Guide for safe design of plant. Canberra: SWA.

Sanders, J. M., Bucher, J. R., Peckham, J. C., Kissling, G. E., Hejtmancik, M. R., & Chhabra, R. S. (2009). Carcinogenesis studies of cresols in rats and mice. *Toxicology*, *257*(1–2), 33–39. https://doi.org/10.1016/j.tox.2008.12.005.

Schinkel, J., Fransman, W., Heussen, H., Kromhout, H., Marquart, H., & Tielemans, E. (2010). Cross-validation and refinement of the Stoffenmanager as a first tier exposure assessment tool for REACH. *Journal of Occupational and Environmental Medicine*, *67*(2), 125–132. https://doi.org/10.1136/oem.2008.045500.

Schinkel, J., Fransman, W., McDonnell, P. E., Klein Entink, R., Tielemans, E., & Kromhout, H. (2014). Reliability of the advanced REACH tool (ART). *Annals of Occupational Hygiene*, *58*(4), 450–468. https://doi.org/10.1093/annhyg/met081.

Smith, T., Sonnenfeld, D. A., & Pellow, D. N. (2007). Challenging the chip: Labor rights and environmental justice in the global electronics industry. *Contemporary Sociology*, *36*(4), 357–358.

Smith, V., & English, J. (2012). The electronics industry. In: T. Rustemeyer, P. Elsner, S. M. John, H. I. Maibach (Eds.). *Kanerva's occupational dermatology* (pp. 661–674). Berlin, Heidelberg: Springer.

Sorahan, T., Waterhouse, J. A., McKiernan, M. J., & Aston, R. H. (1985). Cancer incidence and cancer mortality in a cohort of semiconductor workers. *British Journal of Industrial Medicine*, *42*(8), 546–550.

Spencer, P. J., Crissman, J. W., Stott, W. T., Corley, R. A., Cieszlak, F. S., Schuman, A. M., & Hardisty, J. F. (2002).

Propylene glycol monomethyl ether (PGME): Inhalation toxicity and carcinogenicity in Fischer 344 rats and B6C3F1 mice. *Toxicologic Pathology*, *30*(5), 570–579. https://doi.org/10.1080/0192623029010584.

Spinazzè, A., Lunghini, F., Campagnolo, D., Rovelli, S., Locatelli, M., Cattaneo, A., & Cavallo, D. M. (2017). Accuracy evaluation of three modelling tools for occupational exposure assessment. *Annals of Work Exposures and Health*, *61*(3), 284–298. https://doi.org/10.1093/annweh/wxx004.

Tielemans, E., Noy, D., Schinkel, J., Heussen, H., Van Der Schaaf, D., West, J., & Fransman, W. (2008). Stoffenmanager exposure model: Development of a quantitative algorithm. *Annals of Occupational Hygiene*, *52*(6), 443–454. https://doi.org/10.1093/annhyg/men033.

Torres, C., Jones, R., Boelter, F., Poole, J., Dell, L., & Harper, P. (2014). A model to systematically employ professional judgment in the Bayesian Decision Analysis for a semiconductor industry exposure assessment. *Journal of Occupational and Environmental Hygiene*, *11*(6), 343–353. https://doi.org/10.1080/15459624.2013.866713.

U.S. Environmental Protection Agency (U.S. EPA). (1991). Integrated risk information system. Propylene glycol monomethyl ether (PGME*)*. (Last revised: 7/01/1991). Washington, DC: Author.

U.S. Environmental Protection Agency (U.S. EPA). (1998). *Hazardous waste management system: Identification and listing of hazardous waste solvents*. (63 Fed. Reg. 64372 (to be codified at 40 C.F.R. pts. 261)). Washington, DC: Author.

U.S. Environmental Protection Agency (U.S. EPA). (2002). *Toxicological review of phenol (CAS No. 108-95-2): In support of summary information on the Integrated Risk Information System (IRIS) (EPA/635/R-02/006)*. Washington, DC: Author.

U.S. Environmental Protection Agency (U.S. EPA). (2003). Integrated risk information system. Benzene. (Last revised: 4/17/2003). Retrieved from https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=276.

U.S. Environmental Protection Agency (U.S. EPA). (2012a). *Benchmark dose technical guidance (EPA/100/R-12/001)*. Washington, DC: Author.

U.S. Environmental Protection Agency (U.S. EPA). (2012b). Human health risk assessment. Retrieved from https://www.epa.gov/risk/human-health-risk-assessment.

van de Ven, P., Fransman, W., Schinkel, J., Rubingh, C., Warren, N., & Tielemans, E. (2010). Stoffenmanager exposure model: Company-specific exposure assessments using a Bayesian methodology. *Journal of Occupational and Environmental Hygiene*, *7*(4), 216–223. https://doi.org/10.1080/15459621003597488.

Wald, P. H., & Jones, J. R. (1987). Semiconductor manufacturing: An introduction to processes and hazards. *American Journal of Industrial Medicine*, *11*(2), 203–221. https://doi.org/10.1002/ajim.4700110209.

Yang, Y. K. (2006). Optimization of a photo resists coating process for photolithography in wafer manufacturing via design of experiments method. *Microelectronics International*, *23*(3), 26–32. https://doi.org/10.1108/13565360610680730.

Yeh, W.-M., Noga, D. E., Lawson, R. A., Tolbert, L. M., & Henderson, C. L. (2010). Comparison of positive tone versus negative tone resist pattern collapse behavior. *Journal of Vacuum Science & Technology B: Microelectronics and Nanometer*, *28*(6), C6S6–C6S11. https://doi.org/10.1116/1.3518136.

Yoon, C. (2012). Much concern but little research on semiconductor occupational health issues. *Journal of Korean Medical Science*, *27*(5), 461–464. https://doi.org/10.3346/jkms.2012.27.5.461.

Youngflesh, C. (2018). MCMCvis: Tools to visualize, manipulate, and summarize MCMC output. R package version 0.10.0.

Zalk, D. M., & Nelson, D. I. (2008). History and evolution of control banding: A review. *Journal of Occupational and Environmental Hygiene*, *5*(5), 330–346. https://doi.org/10.1080/15459620801997916.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. Summary of Critical Studies Used for the Dose-Response Assessment.
Table SII. Model Summary for Cresol.
Table SIII. Model Summary for Phenol.
Fig. S1. Model summary with benchmark response incorporating a 10% extra risk for cresol's benchmark dose.
Fig. S2. Model summary with benchmark response incorporating a 10% extra risk for phenol's benchmark dose.
Fig. S3. To access the exposure estimation page from the home page, select "inhalation risk assessment" under the "assessment" tab.
Fig. S4. In the product tab select a chemical product from the inventory to be assessed.
Fig. S5. Select the type of task that best describes the activity being assessed.
Fig. S6. Specify the duration of the task and frequency of the task.
Fig. S7. Specify whether the exposure source is close to the worker and whether far-field sources are present.
Fig. S8. Specify the characteristics of the workplace, including information such as working room size, maintenance, cleanliness and control measures.
Fig. S9. Estimated concentration of each component is summarized in four percentiles and a visual cumulative density plot.
Fig. S10. A summary of each component and corresponding daily concentration is displayed.
Fig. S11. Trace plots and density plots of each parameter in MCMC (1 of 2).
Fig. S12. Trace plots and density plots of each parameter in MCMC analysis (2 of 2).
Fig. S13. Gelman-Rubin Plots of each parameter in MCMC analysis.