Incorporation of Occupational Health in the Process Design: The Photoresists in Semiconductor Manufacturing Industries as an Example

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Main Contents

- Current Practices of Occupational Health (Industrial Hygiene)
- Brief Review of Health Risk Assessment
- To Integrate the Current Available Data for Health Risk Assessment: Using Compounds in Photoresists as an Example
- Conclusions and suggestions

Current Practices of Occupational Health (Industrial Hygiene)

Industrial Hygiene is…

Anticipation	Recognition /Evaluation	Controls	Management
▪Commitment ▪Planning ▪Design ▪Training	▪Hazard Identification ▪Exposure Assessment ▪Monitoring Studies ▪Observations	▪Substitution ▪Engineering ▪Administration ▪Personal Protective Equipment	▪Planning ▪Implementing ▪Self Assessment & Auditing ▪Management Review NOTE: EMS principles

Industrial Hygiene Hazard Recognition

- What is the hazard?
- What is the task / activity?
- How much is used?
- How long is it used?
- How toxic is it?
- How dusty is it?
- How volatile is it?
- What type of hazard control is in place?
- How many people are exposed?
- How often are people exposed?

CHEMICAL STRESS AGENTS

- Gases
- Vapours
- Mists
- Dusts
- Fumes

PHYSICAL STRESS AGENTS

- Electromagnetic and ionizing radiation
- Noise
- Vibrations
- Extremes of temperature
- Extremes of pressure

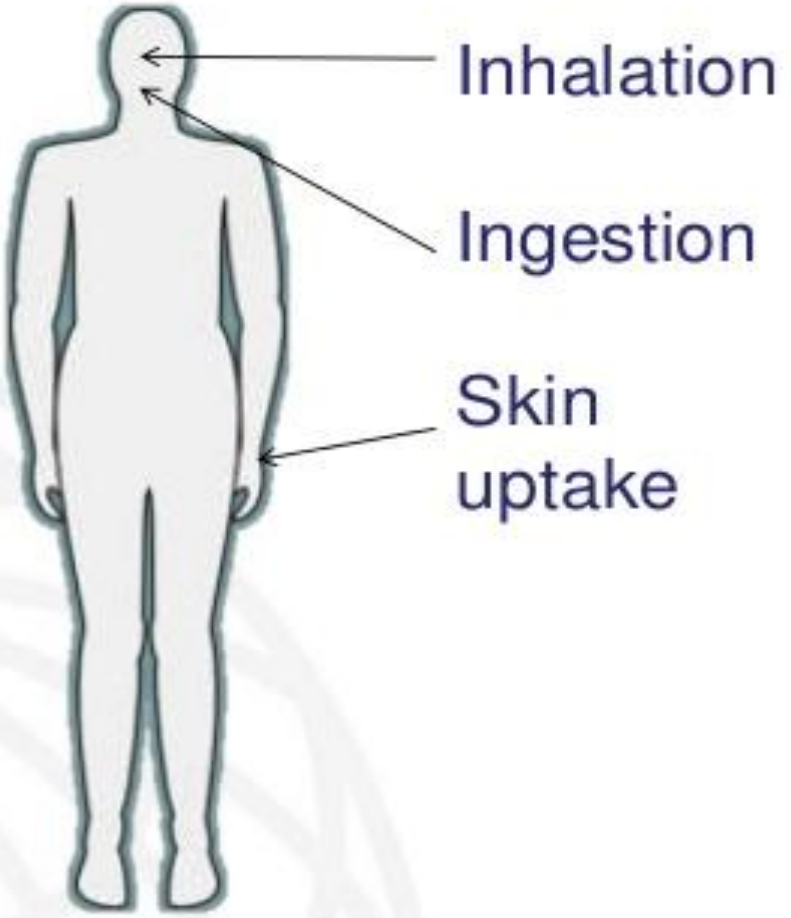
BIOLOGICAL STRESS AGENTS

- Insects
- Moulds
- Viruses
- Fungi
- Bacteria

Routes of exposure…

- Inhalation exposure (mg/m^3)
- Ingestion (mg/day)
- Dermal exposure (mg or mg/cm^2)

- Ideally, we would have all measures on the same basis, i.e. uptake (mg) into the body



Exposure Assessment

Time course is an important factor of exposure because some contaminants are relatively readily metabolized at low levels of exposures but toxic at higher levels of exposure. As such, the dose rate may affect the health outcome.

To account for such differences, exposure assessors focus on magnitude, frequency and duration.

Exposures are also characterized as acute or chronic exposures.

1. Chronic exposures occur over months, years, or even decades and at low levels may manifest non-acute health outcomes.

2. Acute exposures are brief and when they occur at high levels, poisoning or other acute responses may follow.

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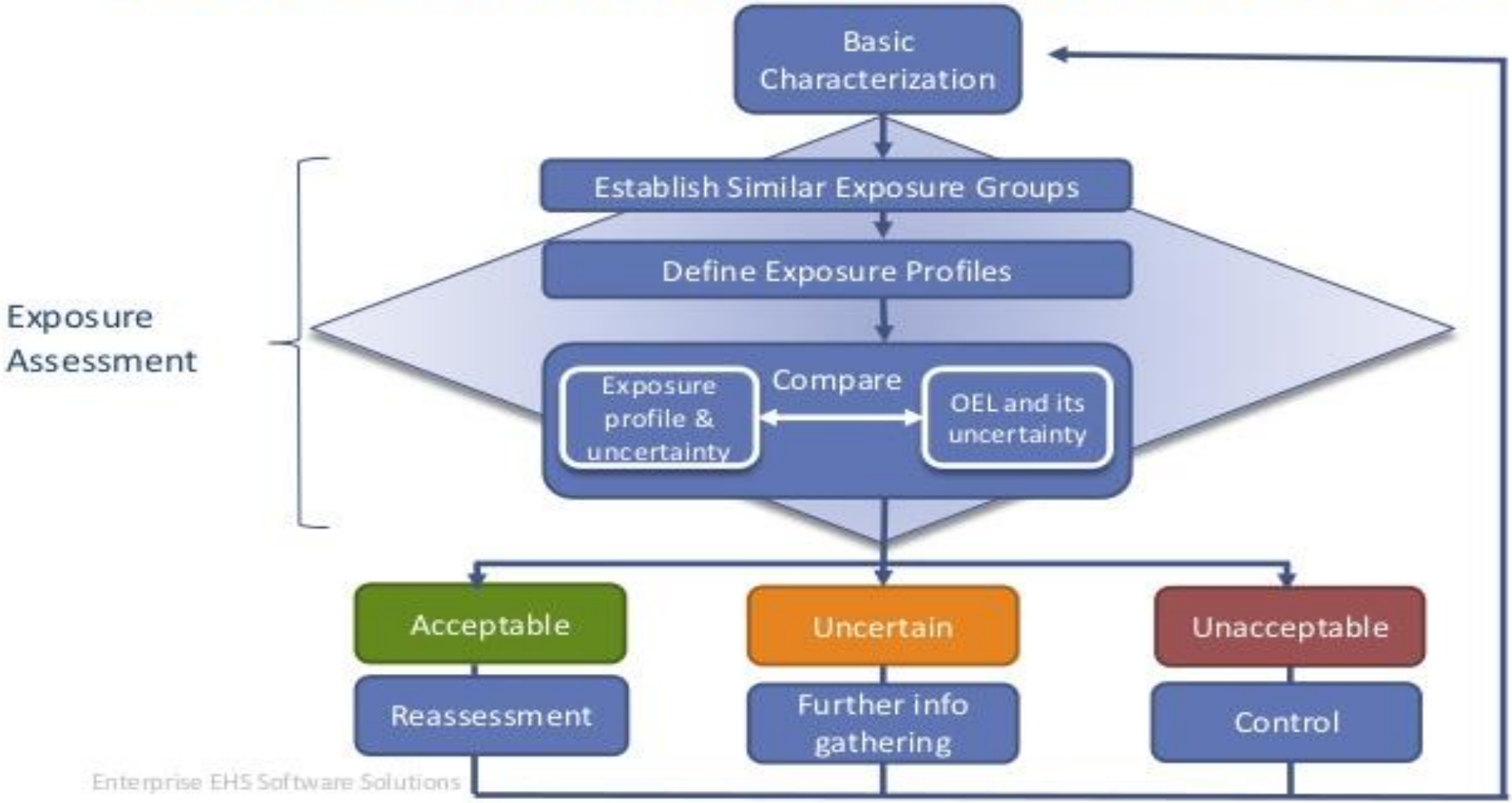
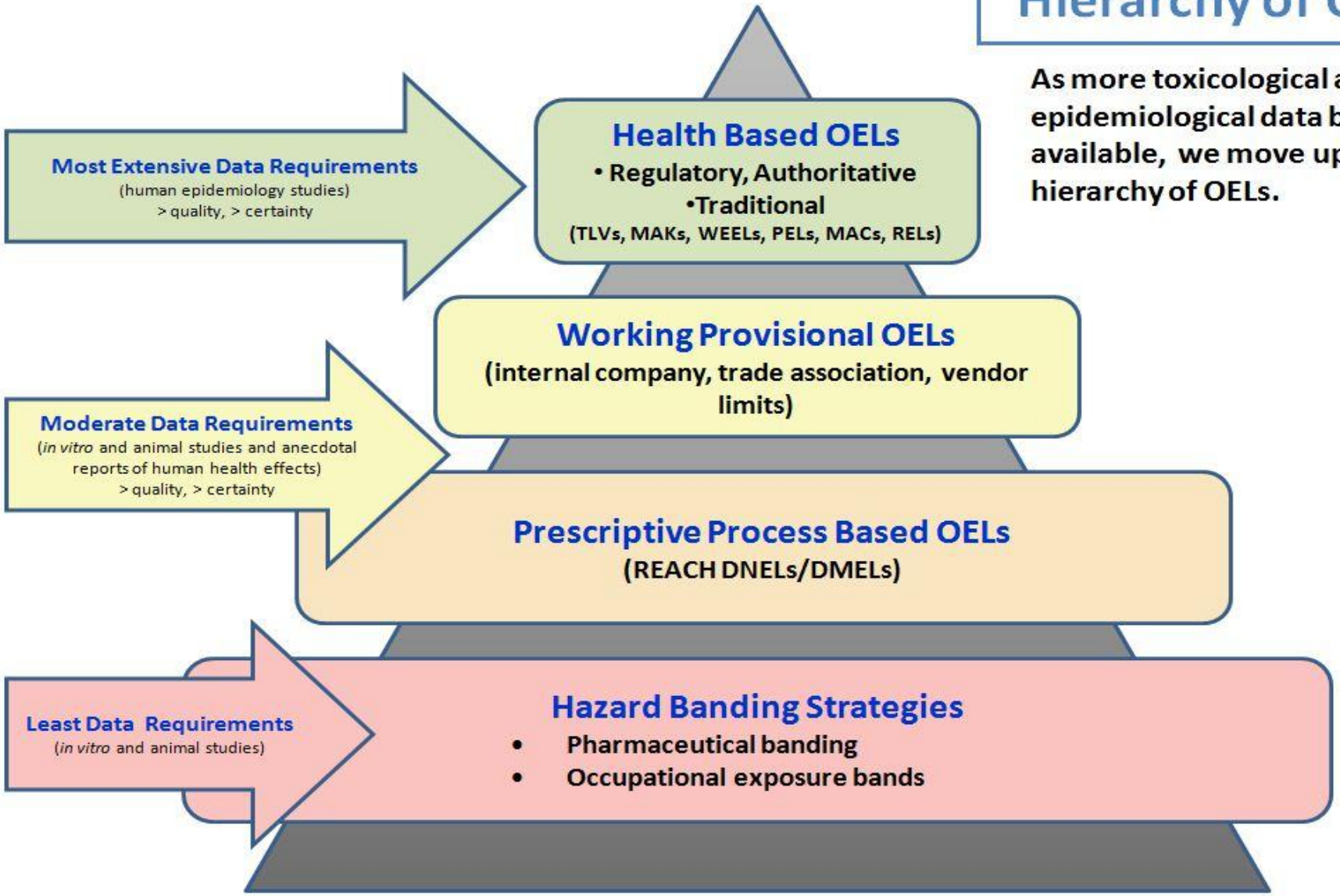
AIHA EXPOSURE ASSESSMENT STRATEGIES



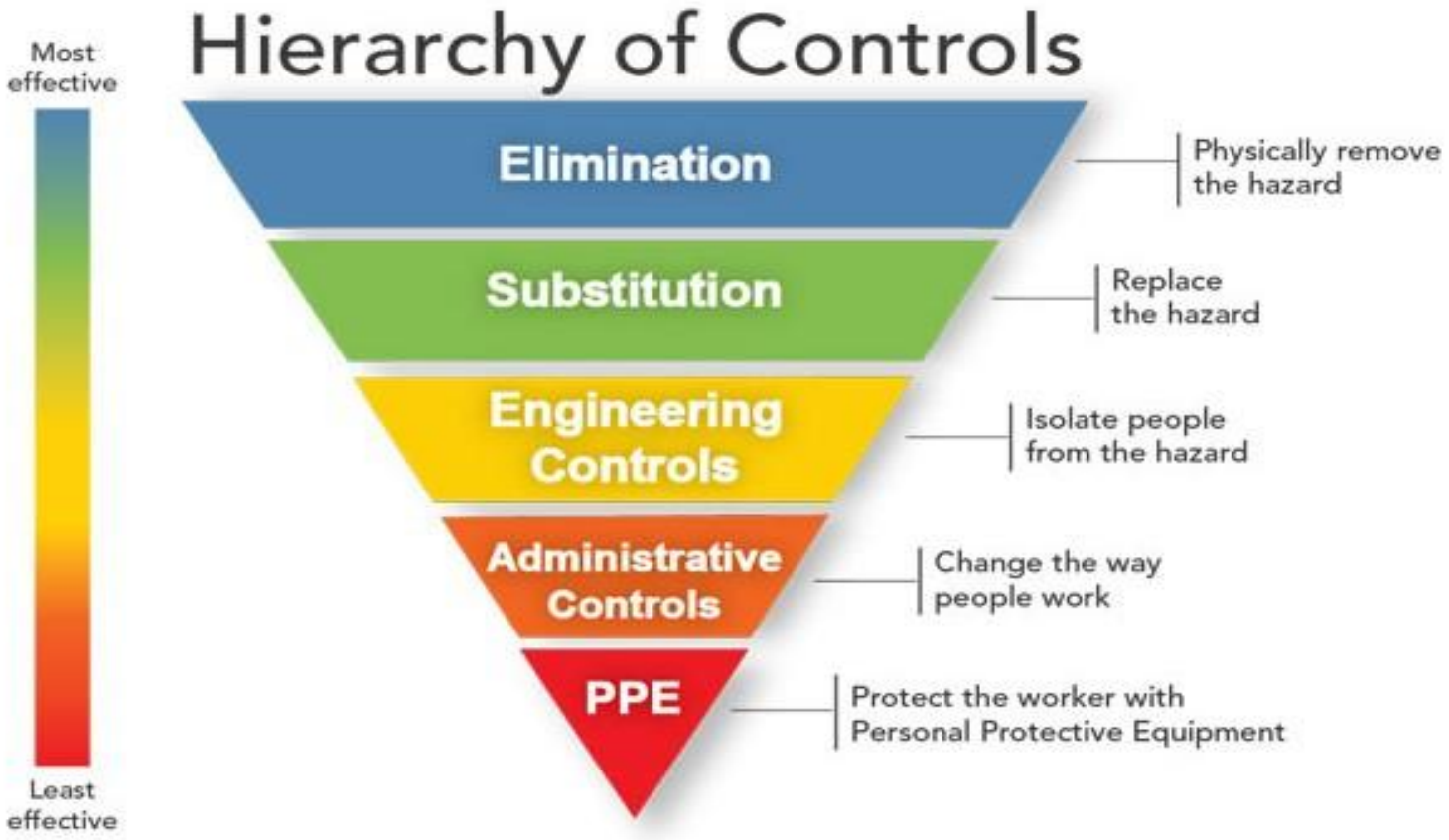
Hierarchy of OELs

As more toxicological and epidemiological data becomes available, we move up the hierarchy of OELs.



Hazard Banding + Exposure Banding → Control Banding

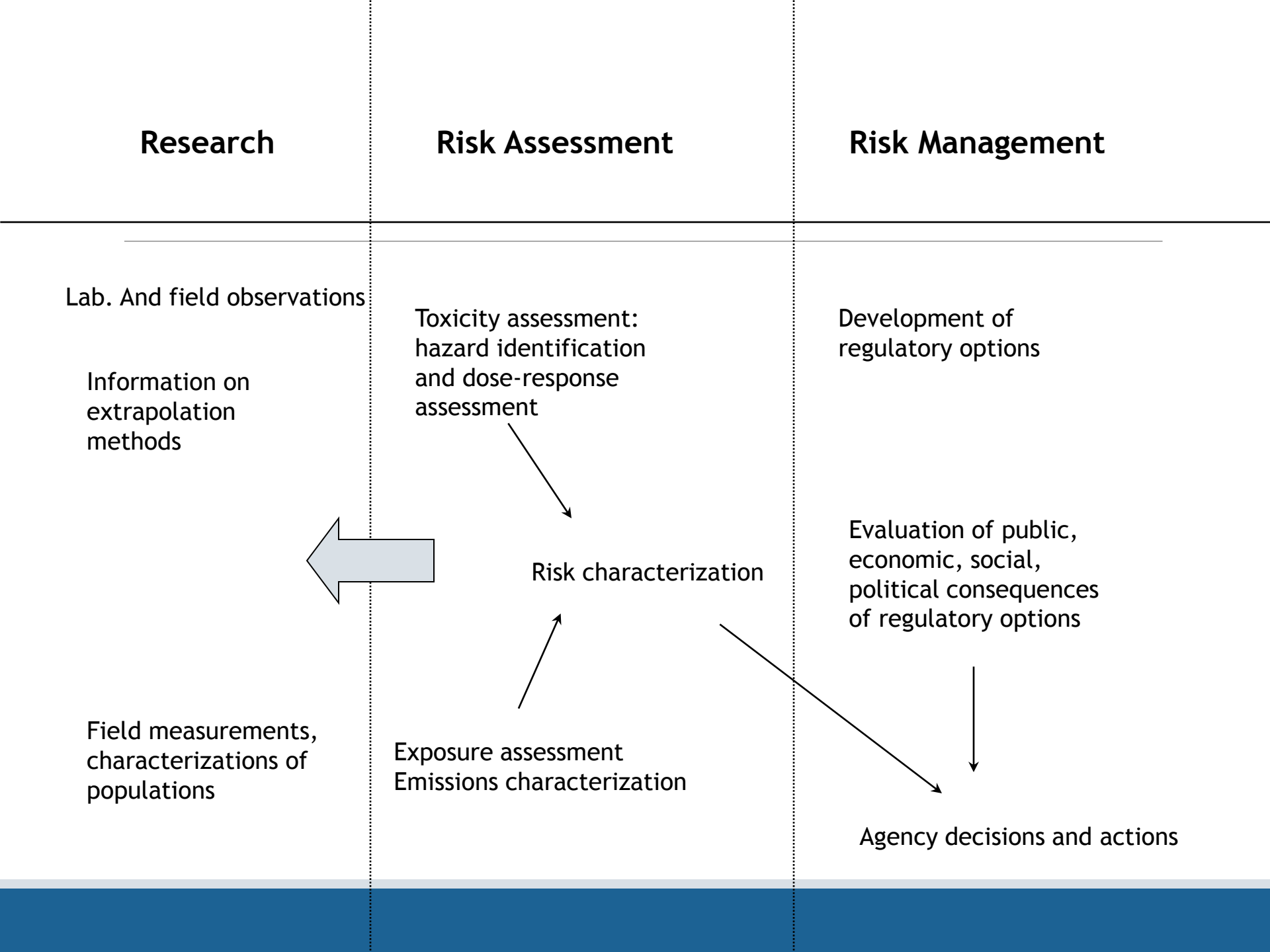
Controlling Exposures to Hazards



High Quantity and Variety of Chemicals

But only a limited number are regulated

Brief Review of Health Risk Assessment


Research
Risk Assessment
Risk Management
Lab. And field observations
Information on extrapolation methods
Toxicity assessment: hazard identification and dose-response assessment
Development of regulatory options
Risk characterization
Evaluation of public, economic, social, political consequences of regulatory options
Field measurements, characterizations of populations
Exposure assessment
Emissions characterization
Agency decisions and actions

PEL setting in Taiwan

Similar to OSHA in USA, the Occupation Safety and Health Administration under the Ministry of Labor in Taiwan has been mandated to promulgate permissible exposure limits (PELs) to protect workers from the health effects due to exposures to hazardous substances.

The OSHA in Taiwan establishes a PEL committee to set PELs by considering technology feasibility, economic strength, political, and social factors.

Proposition of RELs in Taiwan

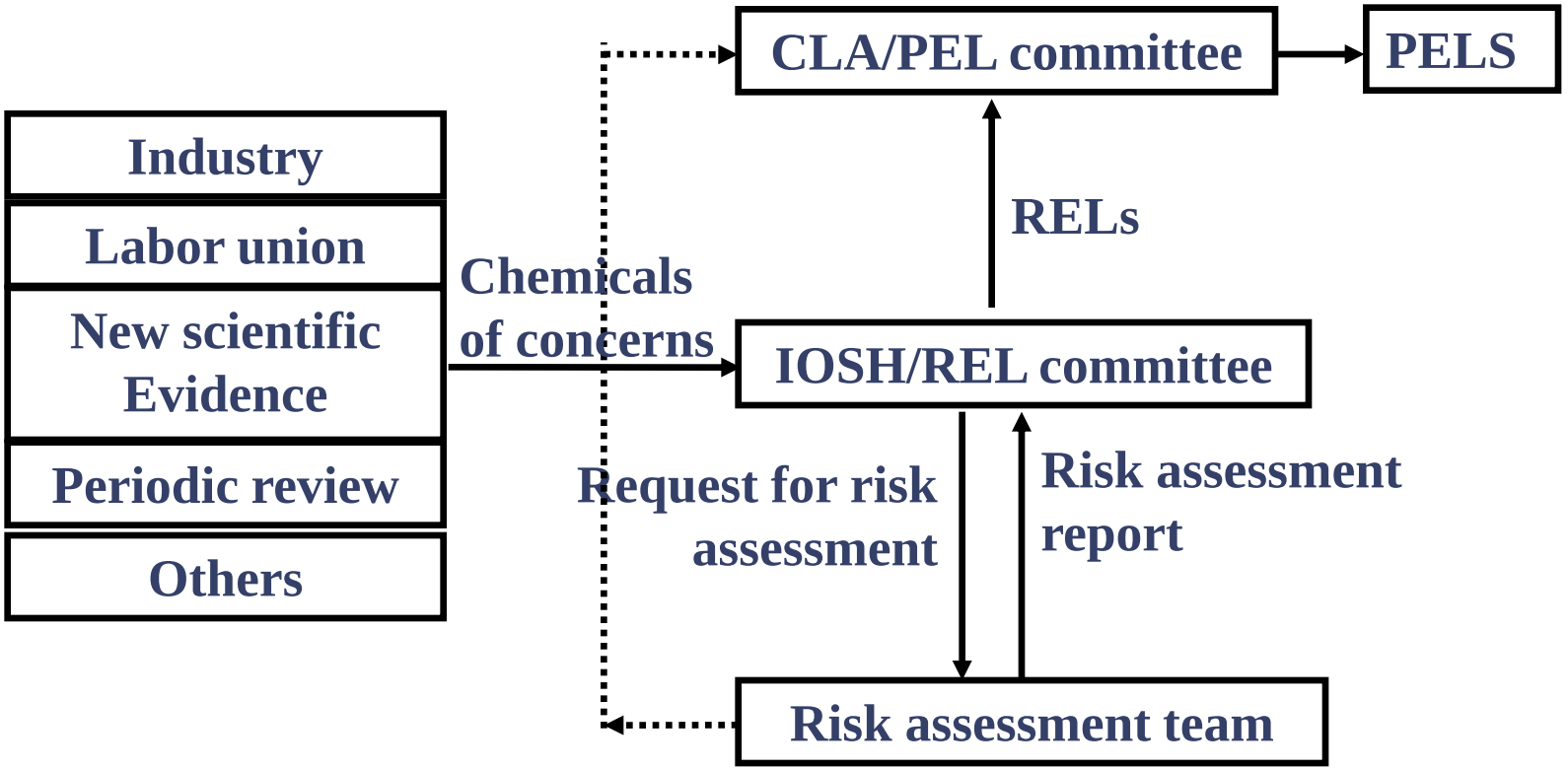
Similar to NIOSH, the Institute of Labor, Occupational Safety and Health (ILOSH) is mandated to develop recommended exposure limits (RELs) by only considering the health effects from exposures to hazardous substances at workplaces.

The REL committee is established by ILOSH to review toxicology and epidemiology data (including worldwide regulations, particularly, US and European countries) to propose new RELs to OSHA in Taiwan.

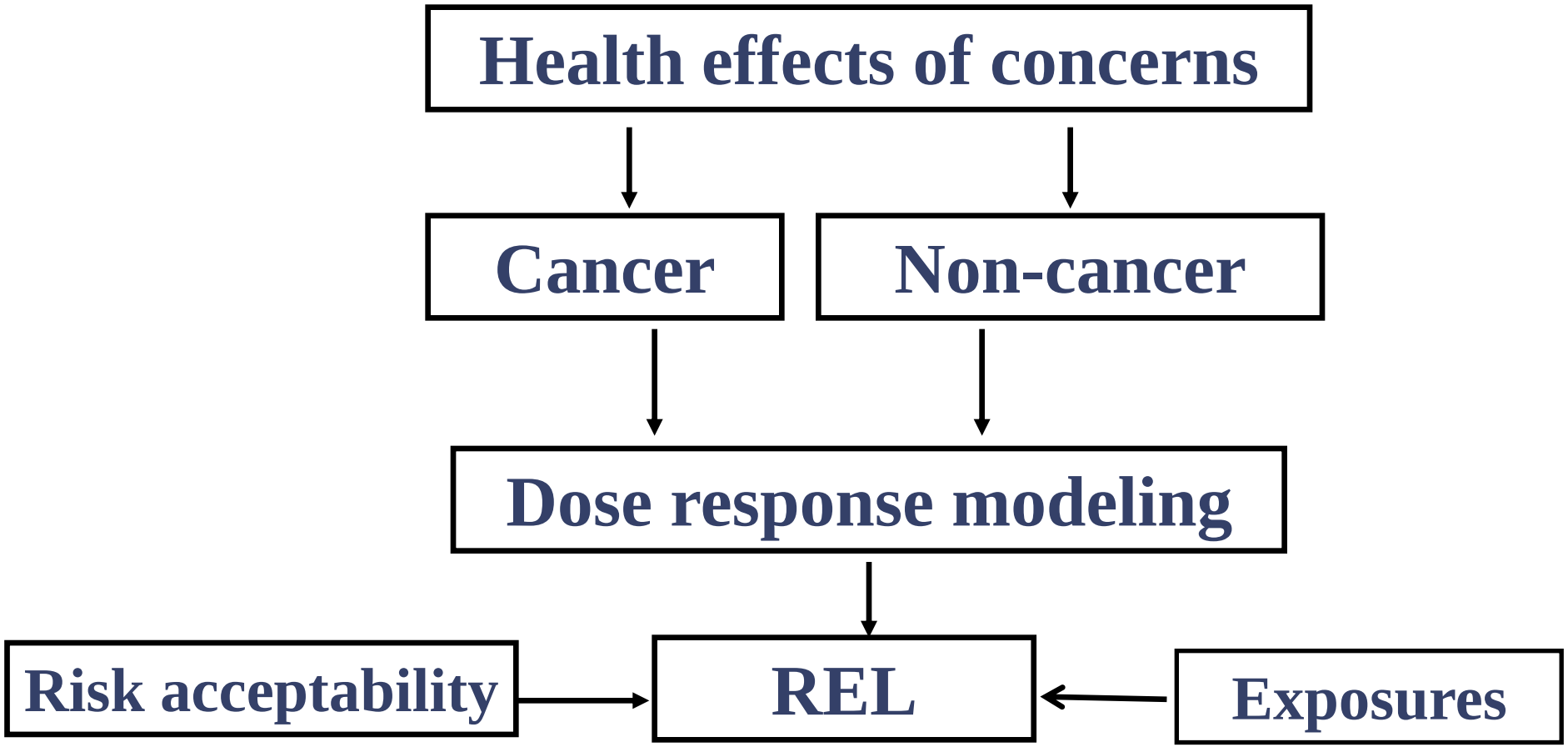
Controversies in the proposition of RELs

- Selection of chemicals for review
- Lack of a systematic review process to evaluate toxicological and epidemiological data
- Lack of a coherent mechanism to propose RELs
- Frequent adoption or modification of ACGIH TLV-TWA, or regulations of OHSA and European countries
- Insufficient scientific supports for the proposed RELs

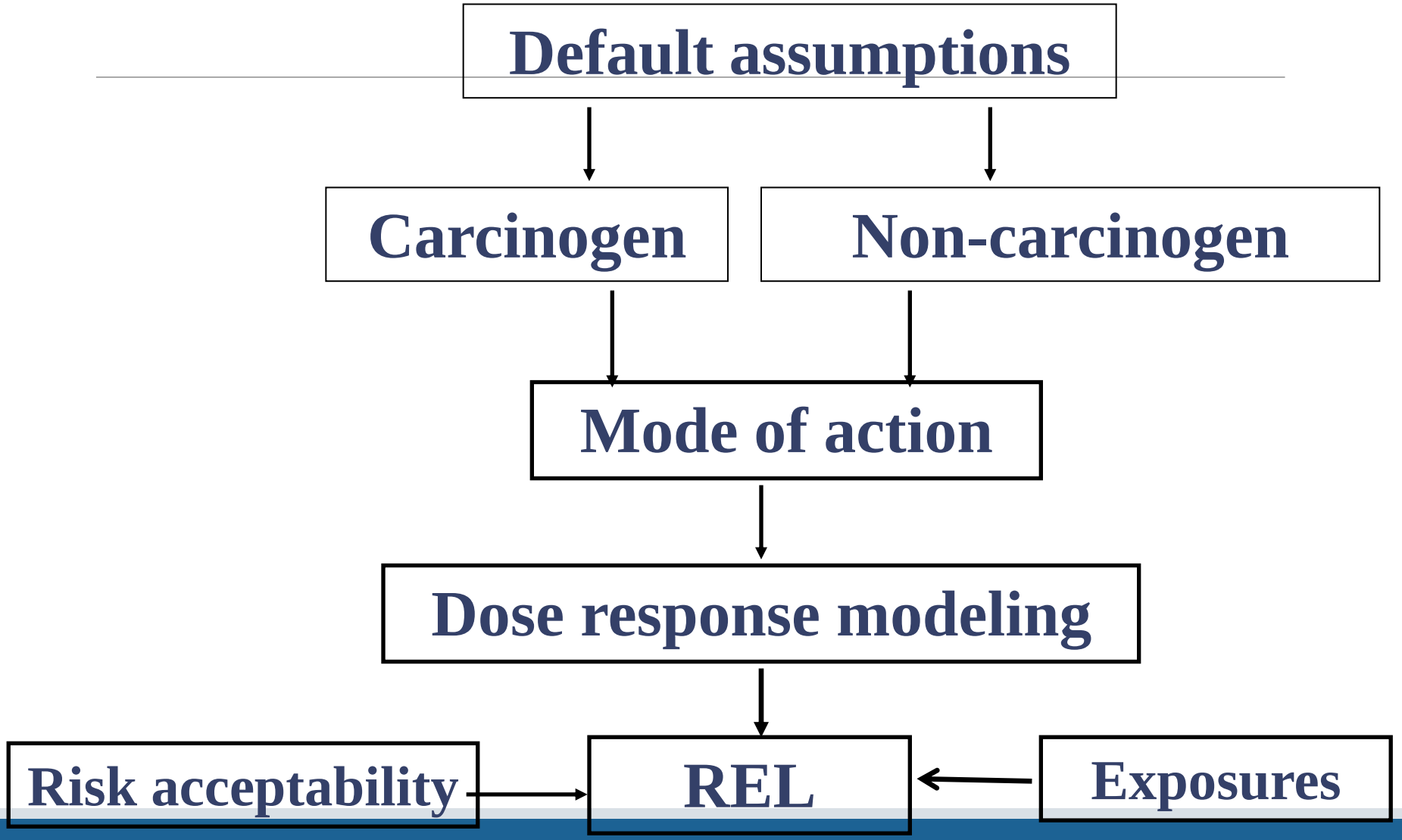
Incorporation of risk assessment into the existing PEL setting process



Derivation of risk-based RELs using epidemiology data



Derivation of risk-based RELs using animal data



REL assessed for hazards in workplaces

Chemical	REL (mg/m^3)	ACGIH(2001)	Taiwan PEL
砷化氫 (Arsine)	RfC：0.0782	0.05 ppm (0.16 mg/m^3)	—
砷 (Arsenic)	1.204×10^{-4}	0.01 mg/m^3	0.5 mg/m^3
1,3-丁二烯 (1,3- butadiene)	16.9	2ppm (4.4 mg/m^3)	10 ppm
二異氰酸甲苯 (Toluene diisocyanate)	0.094	0.005 ppm (0.036 mg/m^3)	0.005 ppm
鄰－二氯苯 (1,2- dichlorobenzene) 對－二氯苯 (1,4- dichlorobenzene)	1.226 1.028	25 ppm (150 mg/m^3) 10 ppm (60 mg/m^3)	50 ppm 100 ppm

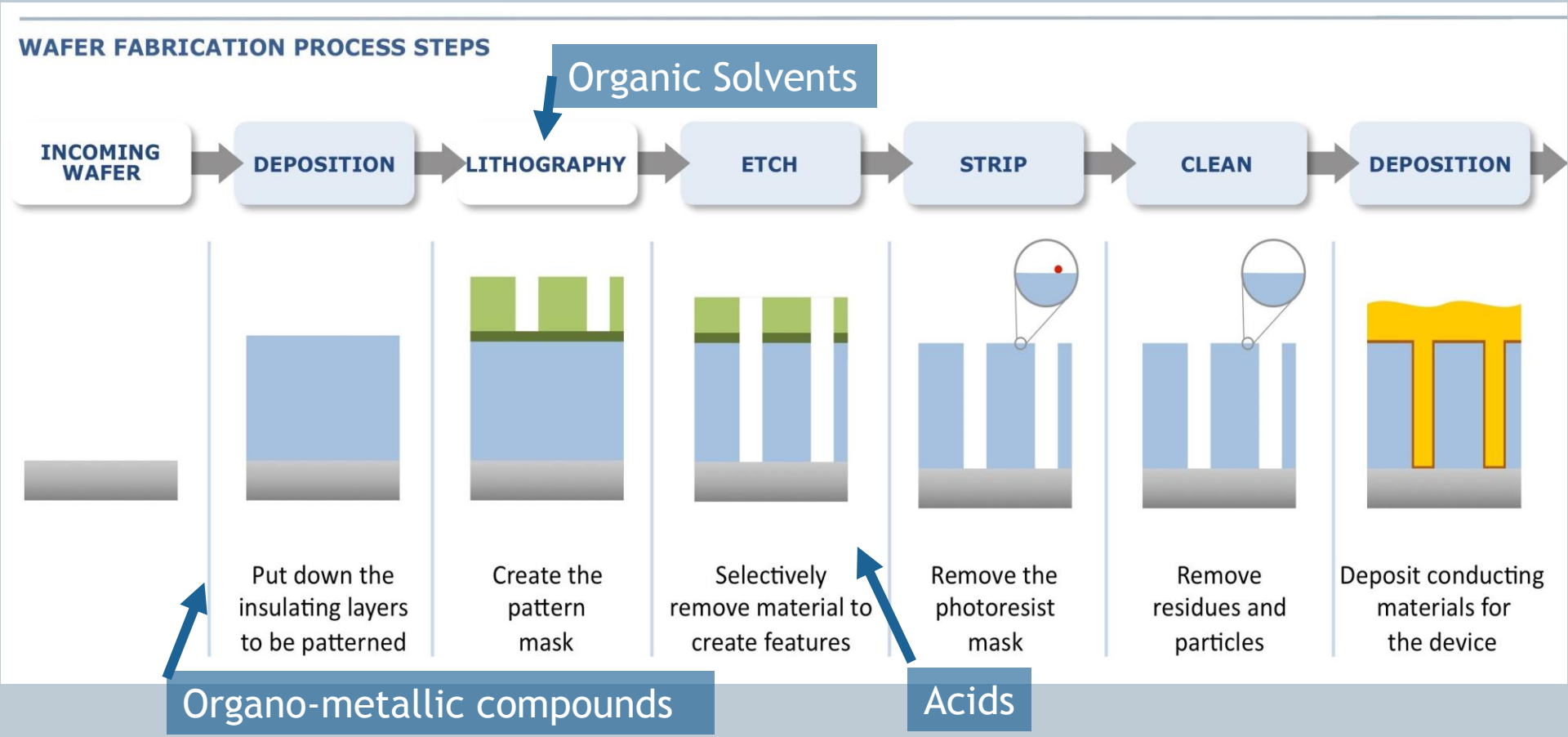
REL assessed for hazards in workplaces

Chemical	REL(mg/m^3)	ACGIH(2001)	Taiwan PEL
氯乙烯 (vinyl chloride)	7.016	1 ppm (2.6 mg/m^3)	5 ppm
鎘 (Cadmium)	3.26×10^{-5}	0.01 mg/m^3	0.05 mg/m^3
三價鉻 (Chromium(III))	1.09×10^{-2}	0.5 mg/m^3	—
苯 (Benzene)	3×10^{-4}	0.5 ppm (1.6 mg/m^3)	5 ppm (皮膚、瘤)
苯乙烯 (Styrene)	1.00	20 ppm (85 mg/m^3)	50 ppm (皮膚)

Current practices in Taiwan

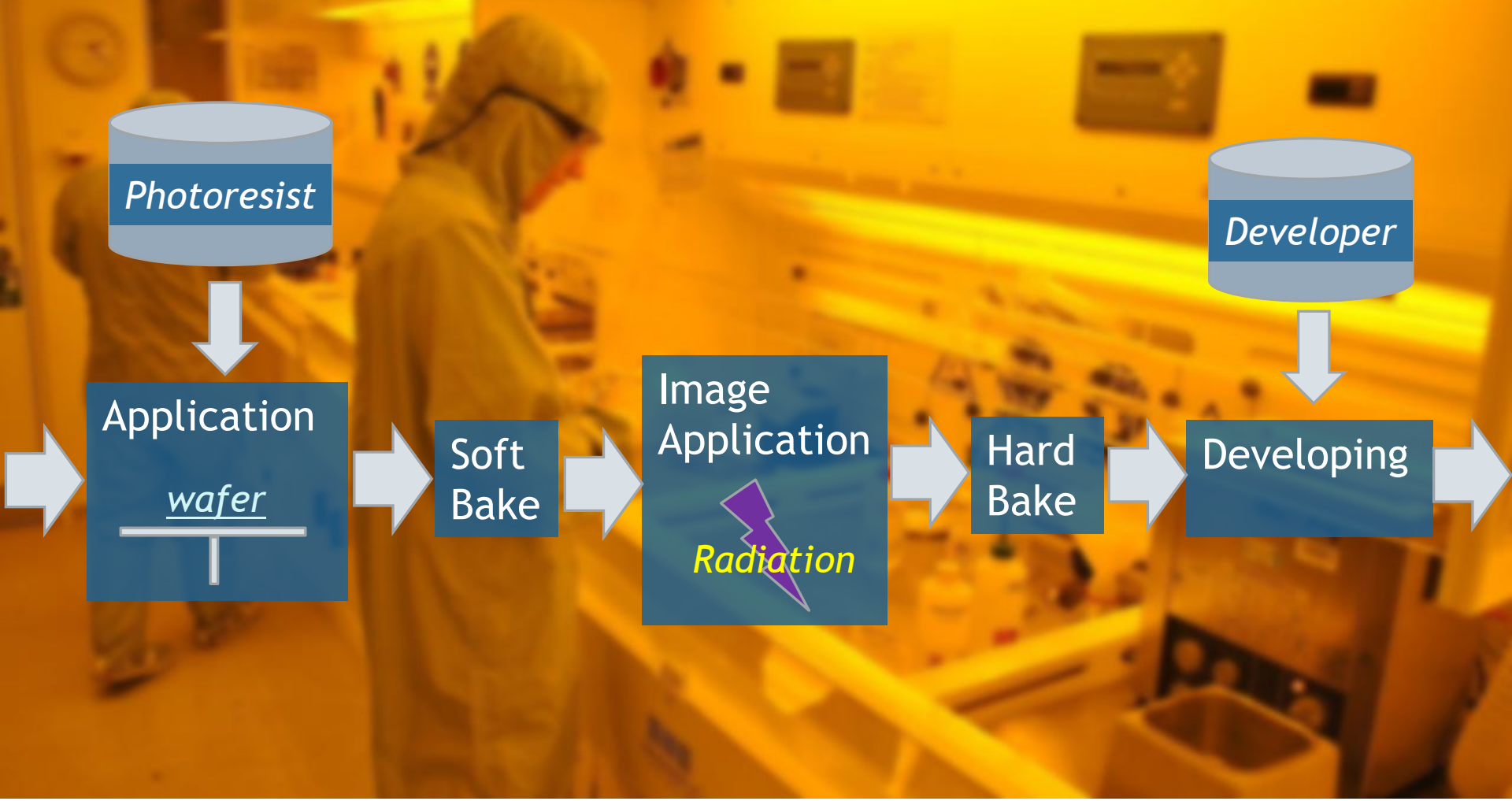
- Majority of companies comply with the current Taiwan PELs and regulations
- The current PELS could not provide sufficient protection to workers
- Control measures on hazards in workplaces include ventilation and personal protection equipment, very few available effective measures to reduce exposures to hazards in workplaces.
- Control measures may have impacts on production so as to be reluctantly put into practices

To Integrate the Current Available Data for Health Risk Assessment: Using Compounds in Photoresists as an Example



LED Manufacturing Process

Epitaxy, Photolithography, Etching, Deposition



Photolithography

Suspected of being weak mutagen, Kidney and liver damage, Teratogen

Chemical Control Banding

A Simplified Qualitative Screening Tool

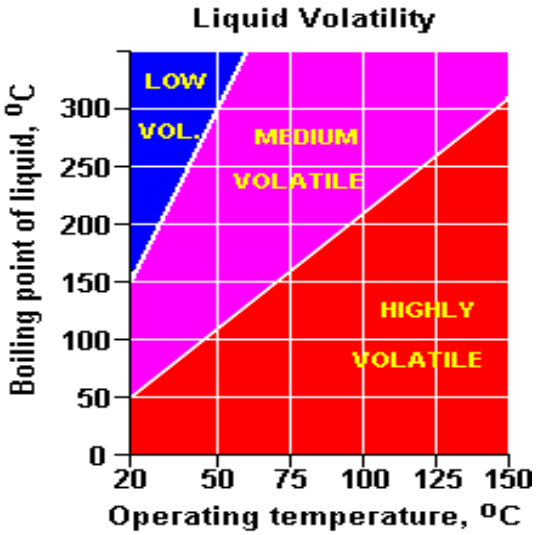
Hazard Classification

Hazard Group (w/ examples)
A - Skin and eye irritants
B - Harmful on single exposure
C - Severely irritating & corrosive; skin sensitizers
D - Very toxic on single exposure; reproductive hazard
E - Carcinogens, asthmagens

Scale of Use

Volatility	Scale of Use
< 1L	Small
1L ~ 1000L	Medium
> 1000L	Large

Ability to become airborne



Screening

Name	Hazard Band	Operation Machine	Operating Temperature (°C)	Boiling Point	Volatility	Scale of Use	Overall Rating
Photoresist EPG-***	D+S	Photoresist Application	90~150	146	H	M	24
Negative Photoresist DNR-****	C+S	Photoresist Application	90~150	120/ 156	H	M	18
Developer TMAH 2.35%	D+S	Developer	20	100	M	M	16
H.M.D.S.	D+S	Vapor Prime Oven	150	127	H	S	12
Photoresist APR ****	A+S	Photoresist Application	90~150	146	H	M	6
Thiner AZ EBR**	A+S	Photoresist Application	90~150	124	H	M	6
Acetone	A+S	Cleaner	20	56.2	M	M	4
IPA	A+S	Cleaner	20	82.3	M	M	4
Ethanol	A+S	Cleaner	20	78.4	M	S	2

SDS of Photoresist

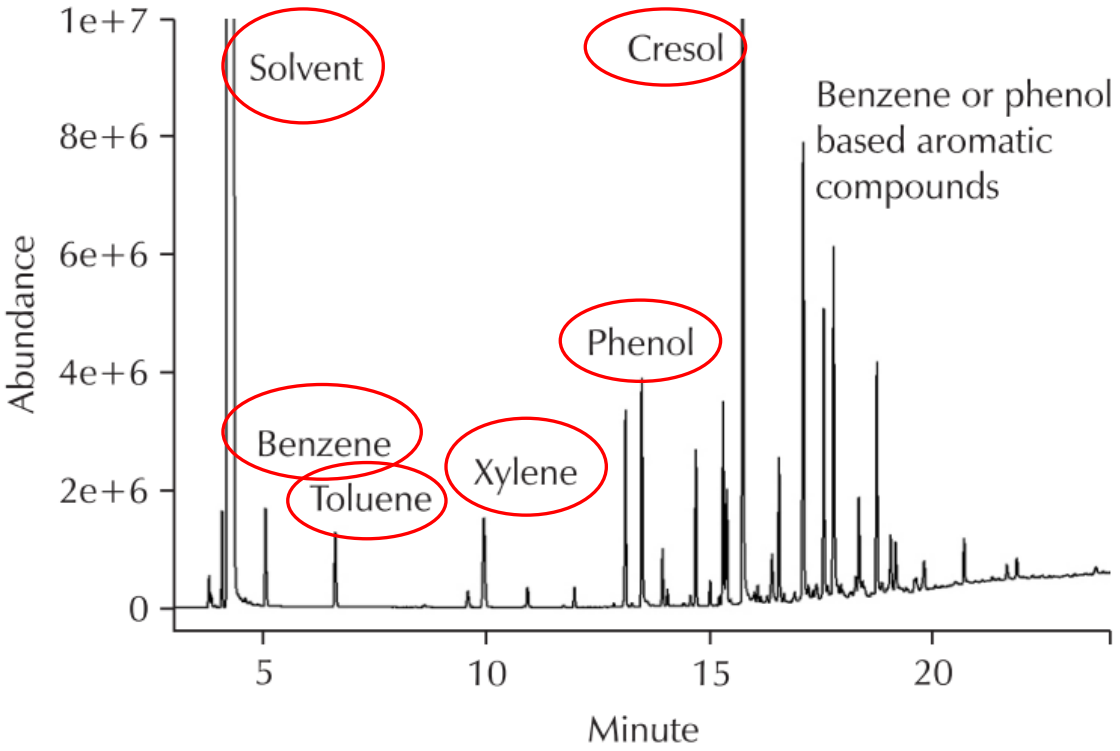
Compound	CAS No.	Composition
Solvent Propylene Glycol Monomethyl Ether Acetate (PGMEA)	108-65-6	50%~80%
Novolak Resin	N/A	10%~35%
Photoactive Compound (Diazonaphthaloquinone, DNQ)	N/A	0.1~0.5%

- Limited toxicological study available (NTP, 2006)
- By design should have low volatility (OECD, 2010; Claussen, 2001)

Composition and Potential By-products of Photoresist

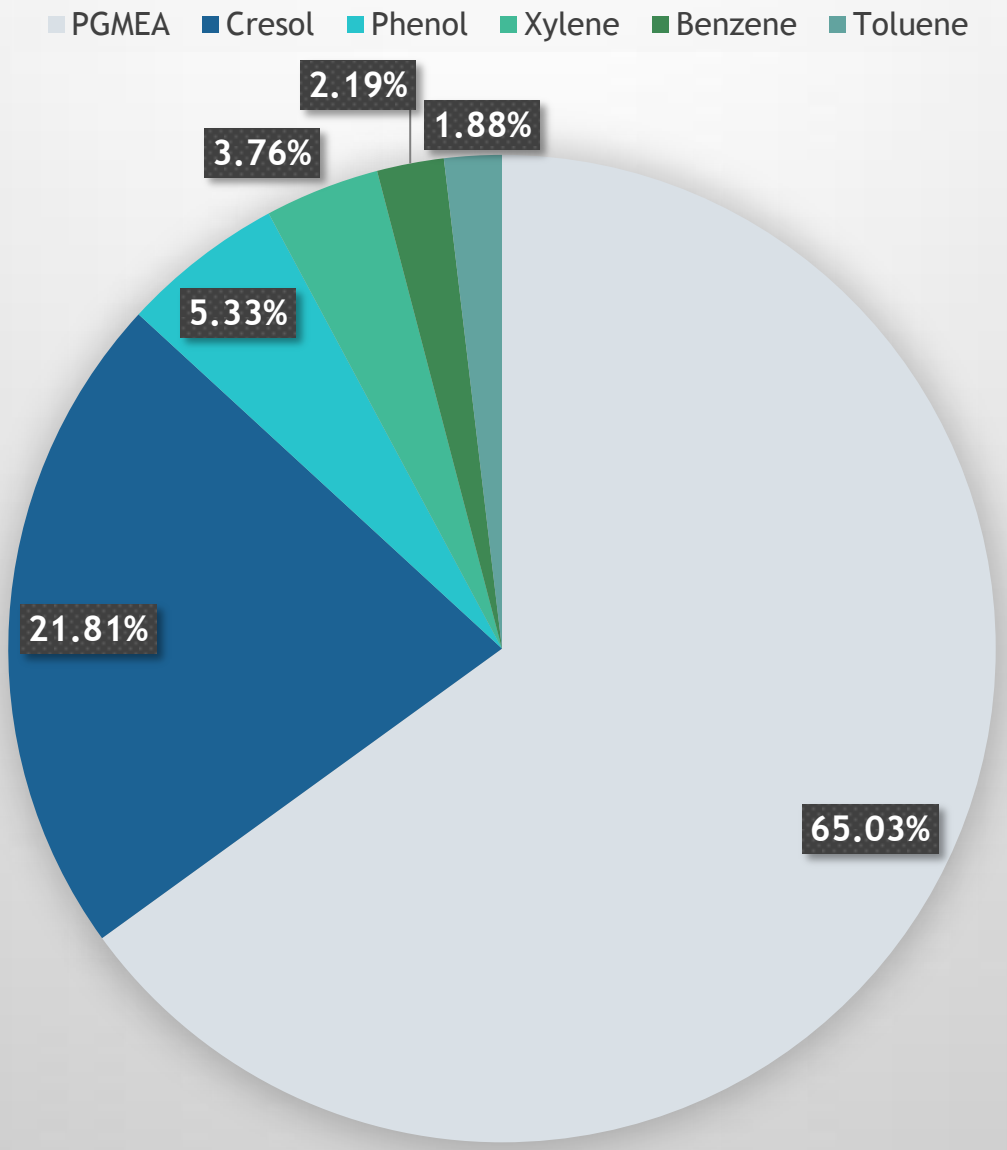
Photochemical reaction when exposed to light
- Ketene
- Carboxylic Acid

Decomposed aromatic compounds
- Simulated by thermal energy [38,39]



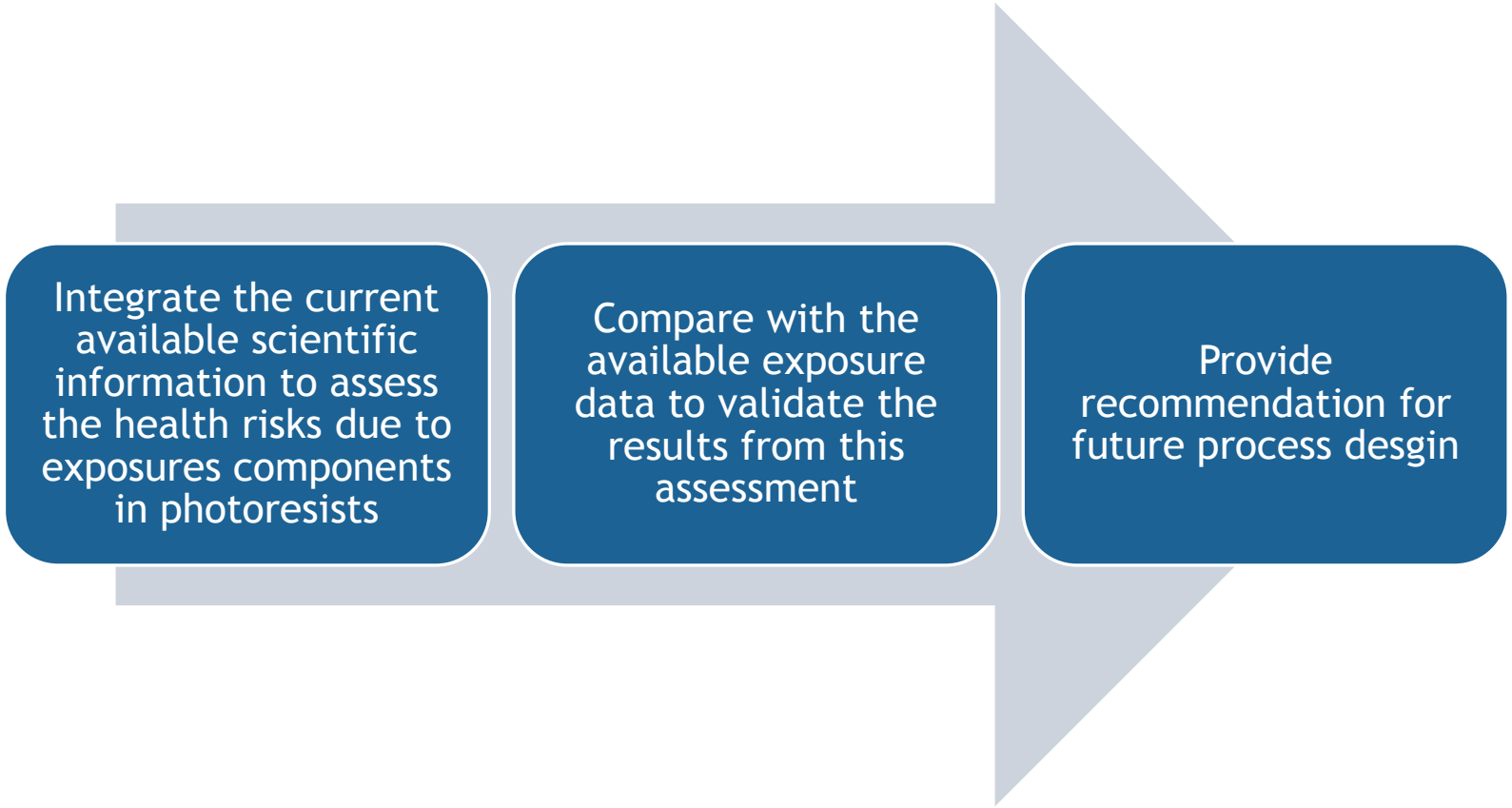
(Park et al, 2011)

Estimated Composition Percentage

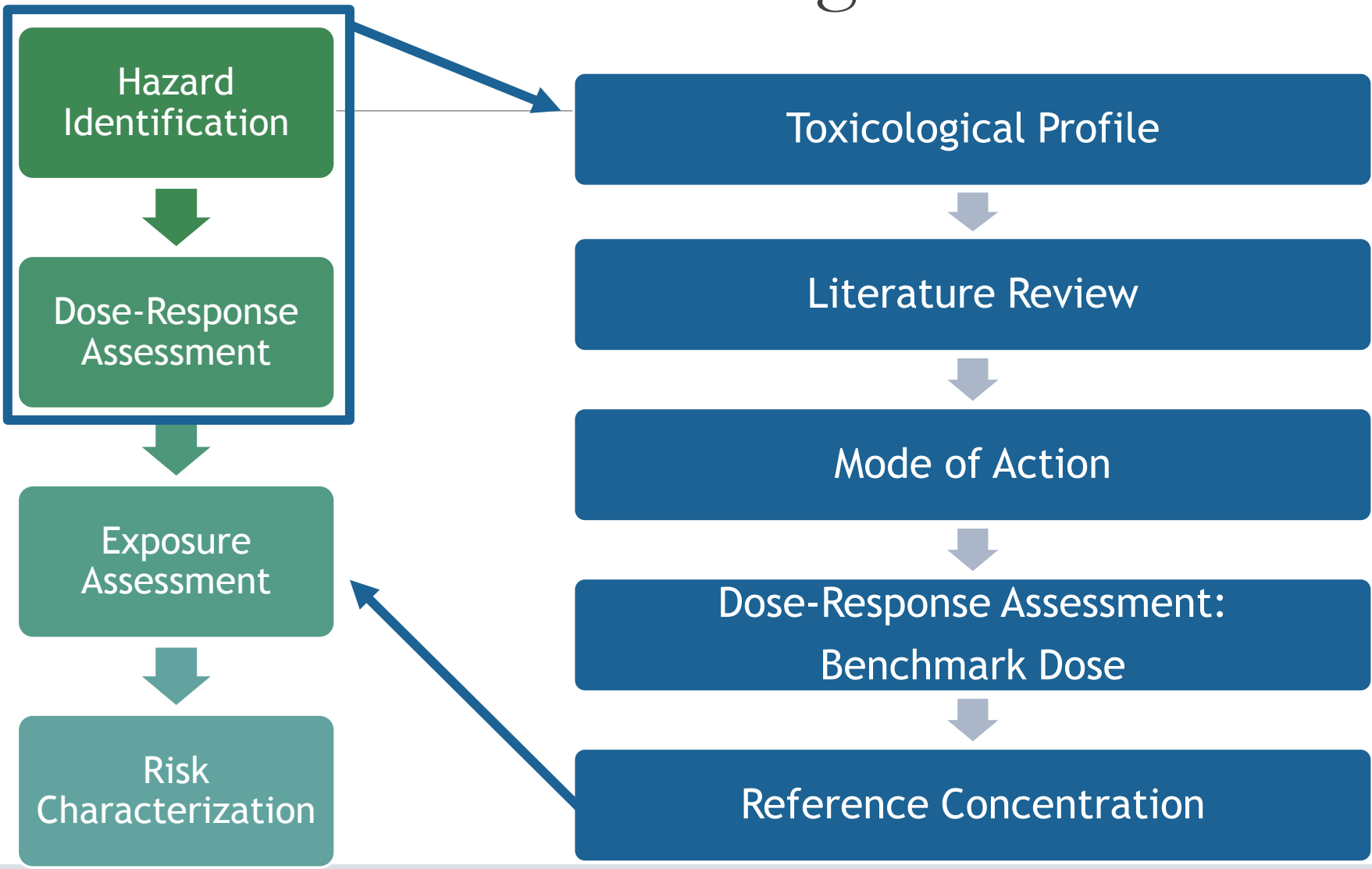


Estimated from Park et al. (2011)

Objective


Integrate the current available scientific information to assess the health risks due to exposures components in photoresists
Compare with the available exposure data to validate the results from this assessment
Provide recommendation for future process desgin

Risk Assessment Paradigm



Reference Concentration

$$\mathrm{RfC} = \mathrm{BMDL} \times MF_{intra} \times MF_{inter} \times MF_{subchronic} \times MF_{data}$$

$$\text{Cancer Slope Factor} = \frac{\mathrm{BMR}}{\mathrm{BMDL}}$$

Uncertainty Factors	**MF**
Inter-species extrapolation	10
Human variability in sensitivity	10
Sub-chronic to Chronic	10
Completeness of database	1-10

Stoffenmanager

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for occupational exposure
assessment and risk control

www.stoffenmanager.nl

An extension of control banding:

$$C_t = \left\{ (E \times a) + \left(E \times H \times \eta_{lc} \times \eta_{gv_{nf}}\right) + (E \times H \times \eta_{lc} \times \eta_{gv_{ff}}) \right\} \times \eta_{imm}$$

where

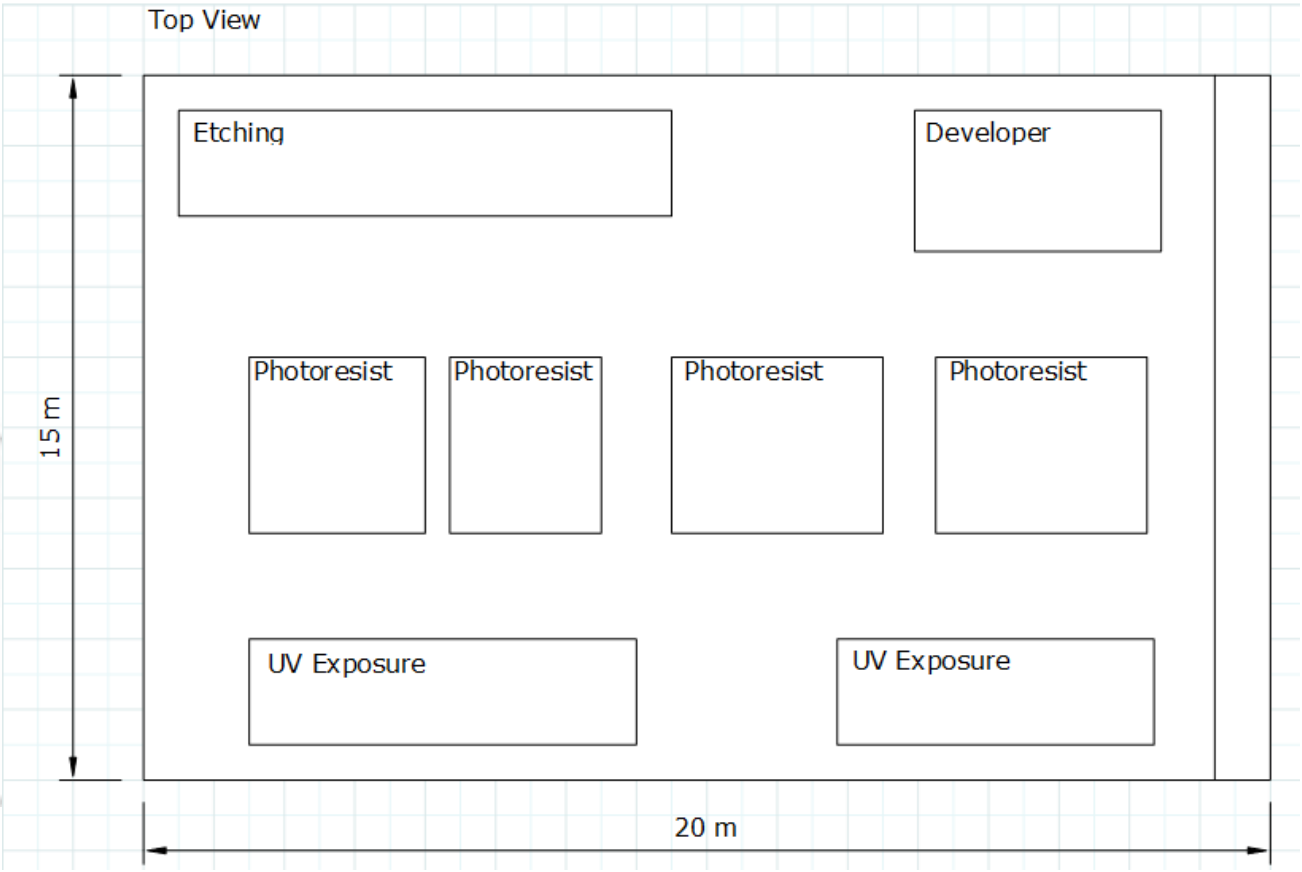
- E = Intrinsic emission (vapor pressure)
- a = background concentration
- H = Handling
- η_{lc} = Local control measures
- η_{gv} = General ventilation (near/far-field)
- η_{imm} = Separation

Exposure Setting (Top View)

-30 Air Changes per Hour

-Containment

-Local exhaust



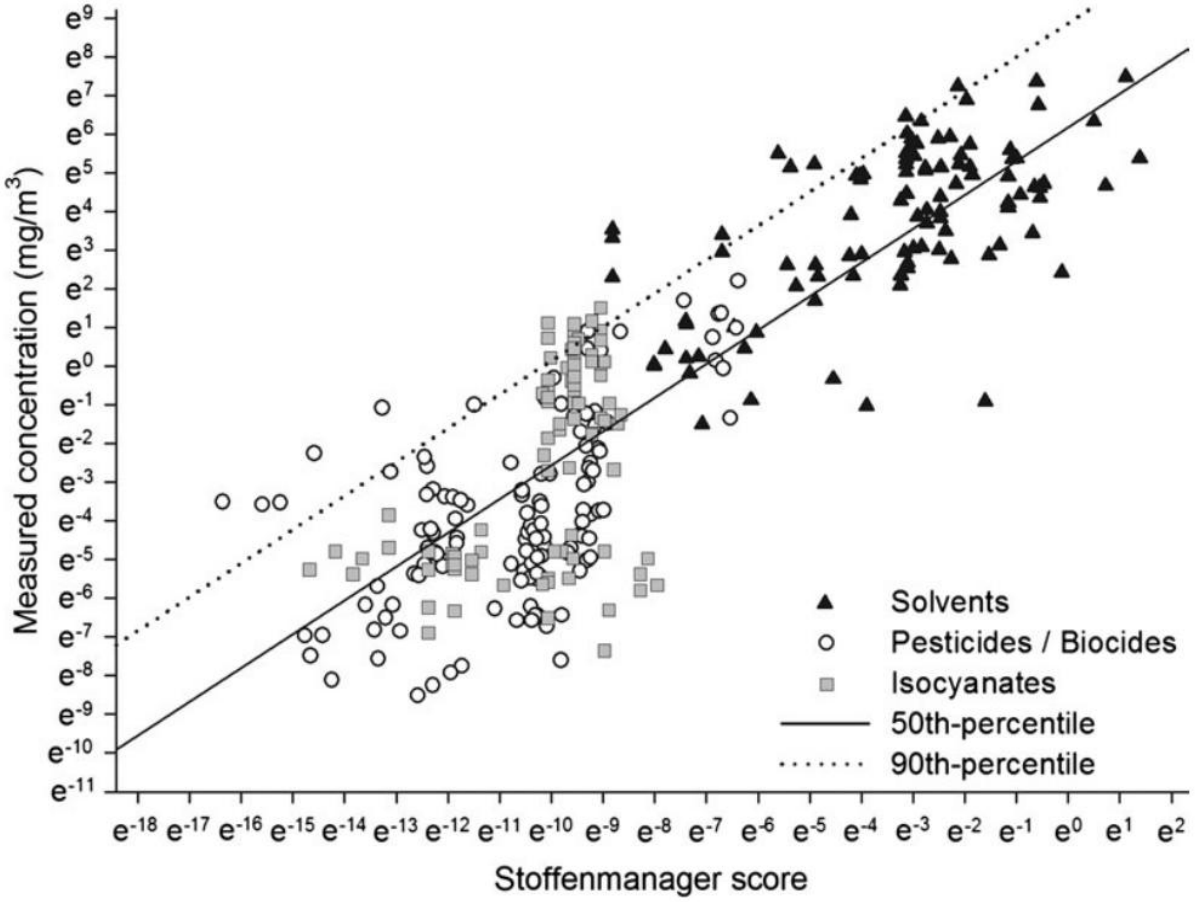
Input Parameters

Working conditions

1. Dilution of the product: 100% (Not Diluted)
2. Multiple employees: No
3. Duration of the task: 4 to 8 hours a day
4. Frequency of the task: 4-5 days a week
5. Regular cleaning of work area: No
6. Regular inspection and maintenance: Yes
7. Activity in breathing zone: No
8. Activity: Handling of liquids on small surfaces or incidental handling of liquids.
9. Evaporation, drying or curing after activity: Yes
10. Volume of the working room: Over 100m^3
11. Ventilation working room: General ventilation (mechanical)
12. Control measures at the source: Containment of the source with local exhaust ventilation
13. Segregation of employee: The employee does not work in a cabin
14. Protection of the employee: Half mask respirator with filter/cartridge

Quantification using Mixed-effect Regression

$$\mathrm{Ln}(\mathrm{Y}_{ij}) = X_{ij} = B_0 + B_1 \times Ln(C_t) + \delta_i + \epsilon_{ij}$$



Estimated Concentration:

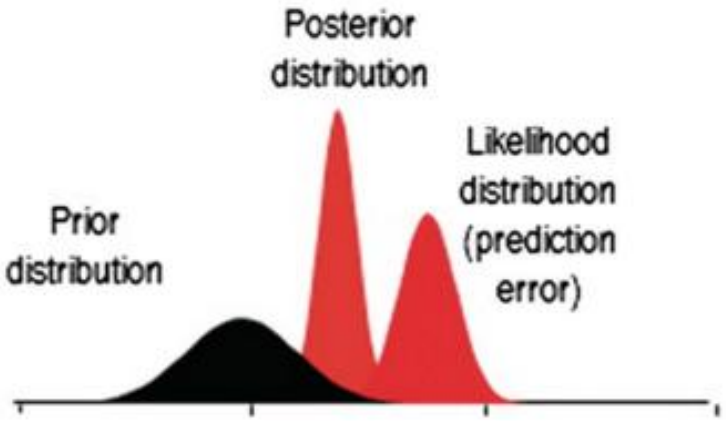
$$\hat{Y} = EXP[B_0 + B_1 \times Ln(C_t)]$$

Percentile Modifier:

$$\mathrm{M} = \mathrm{EXP}\left[\mathrm{Z} \times \sqrt{\sigma_{bc}^2 + \sigma_{wc}^2}\right]$$

Bayesian Inference

$$p(\theta \mid Y) = \frac{p(Y \mid \theta)p(\theta)}{\int p(Y \mid \theta)p(\theta)d\theta}$$



where

$p(\theta)$: Prior Distribution

$p(Y \mid \theta)$: Likelihood function

$p(\theta \mid Y)$: Posterior Distribution

Modeling Estimation

Exposure sampling data

Predictive distribution of future observation

Risk Characterization: Lifetime Average Dose

$$I_{Ih} = \frac{C_a \times EF \times ED}{AT}$$

I_{Ih}: Life time average daily intake

C_a: Estimated concentration in air (mg/m^3)

EF: Exposure frequency (Day/year or hour/day)

ED: Exposure duration (year or day, 35 for occupational)

AT: Average lifetime (70 years)

Risk Characterization:

$$Cancer\ risk = I_{Ih}\ x\ CSF$$

- $Cancer\ risk < 1/1{,}000{,}000$

$$Hazard\ index = I_{Ih}/RfC$$

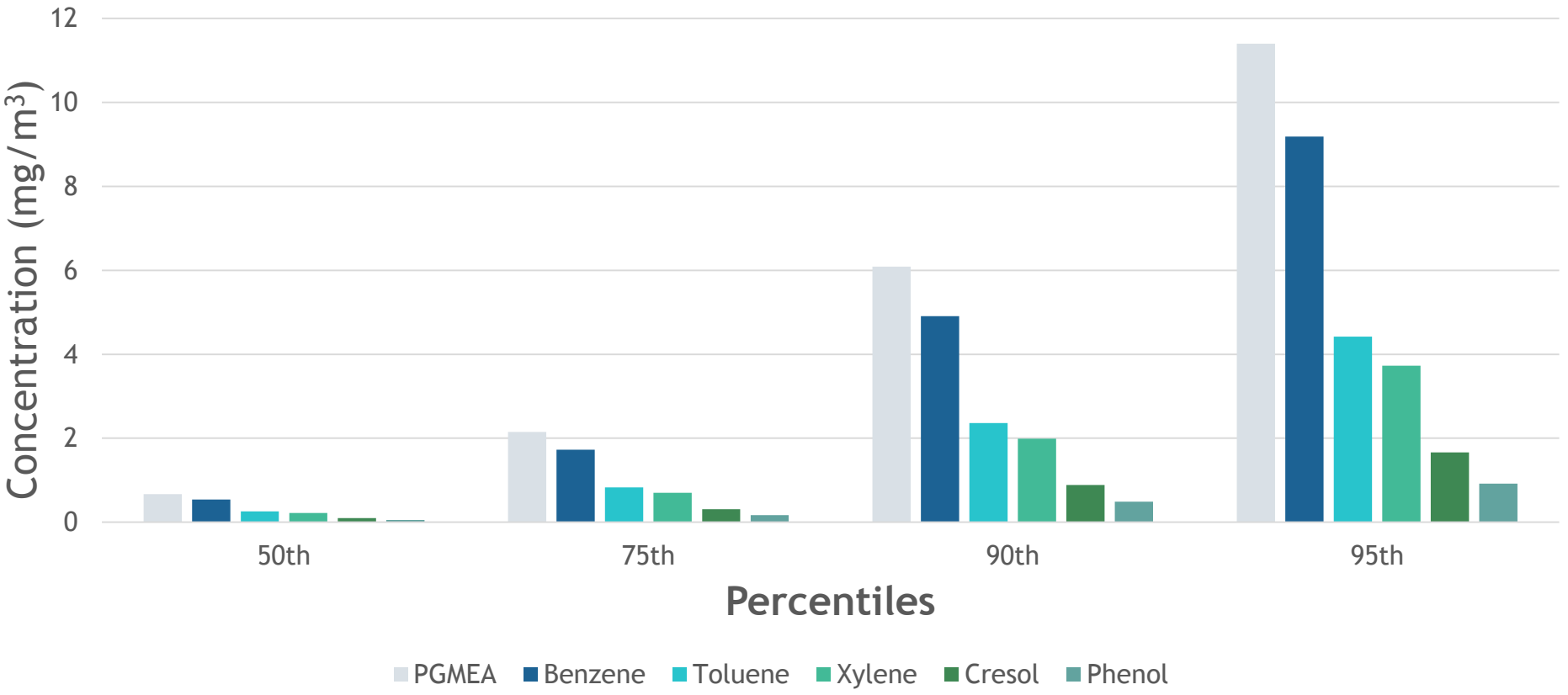
- $Hazard\ index < 1$

Results

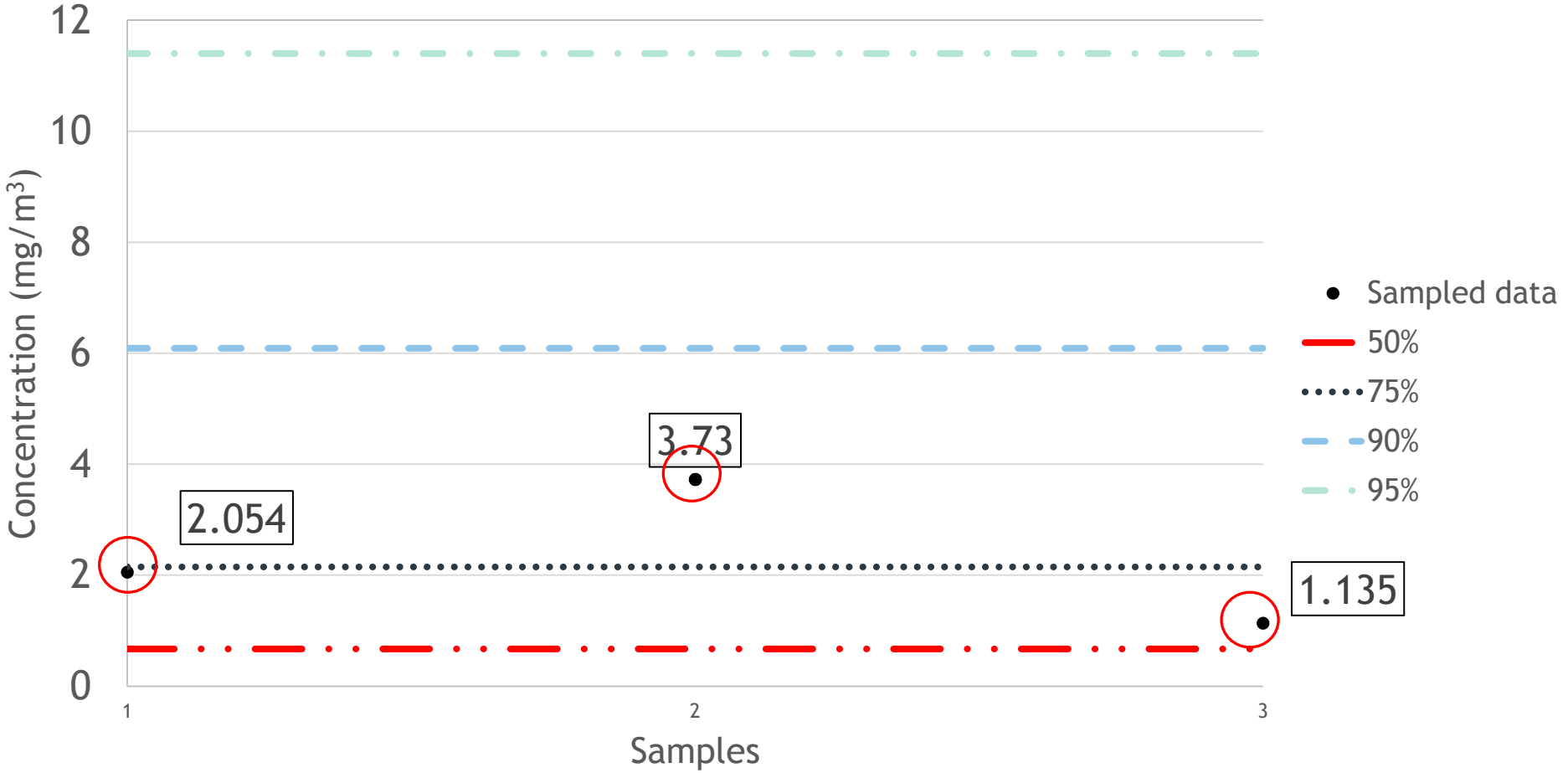
Summary of RfC for each compound

	BMDL	Adjustment Factor	$BMDL_{adj}$	Inter-species MF	Intra-species MF	RfC (mg/m^3)
PGMEA	70.6316 ppm	(6/24 hrs) * (5/7 days)	12.6125 ppm	3	10	1.55
Phenol	0.68251 ppm	(6/24 hrs) * (5/7 days)	0.12188 ppm	10	10	4.69×10^{-3}
Cresol	21.01 mg/kg/day	(60 kg) / (20 L/day) * 0.5	126 mg/m^3	10	10	1.26
Benzene	0.103932 ppm	(8/24 hrs) * (6/7 days)	0.0286 ppm	1	10	9.6×10^{-3}
Toluene	*N/A (Based on Epidemiological NOAEL [IRIS, 2003])*			1	10	5
Xylene	8.75546 ppm (average)	(6/24 hrs) * (5/7 days)	1.563475 ppm	10	10	6.78×10^{-2}

Estimated by-product exposures

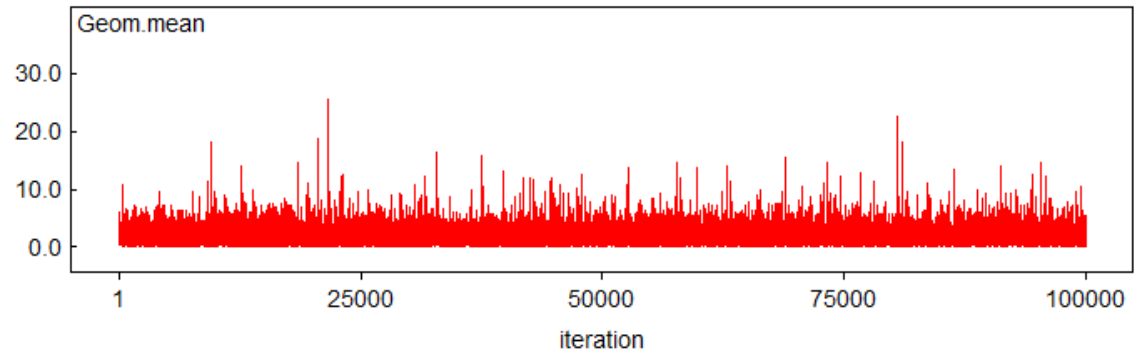


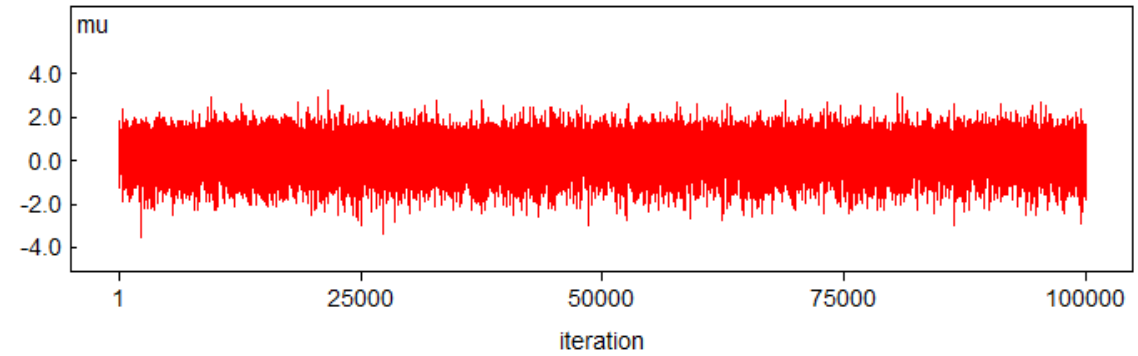
Comparing sampled data with estimated distribution



Posterior Distribution (PGMEA)

node	mean	sd	MC error	2.5%	median	75.0%	90.0%	95.0%	97.5%
Geo.sigma	4.566	5.56	0.05025	0.5598	2.982	5.062	8.927	12.74	18.25
Geom.mean	1.69	1.008	0.00381	0.3544	1.542	2.128	2.821	3.401	4.07
HI_PGMEA	0.1298	0.07742	2.926E-4	0.02722	0.1185	0.1634	0.2166	0.2612	0.3126
mu	0.3578	0.6066	0.003028	-1.037	0.4332	0.7549	1.037	1.224	1.404
sigma	1.184	0.7748	0.007365	-0.5801	1.093	1.622	2.189	2.545	2.904

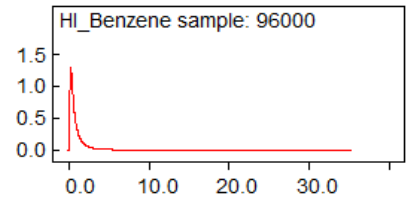


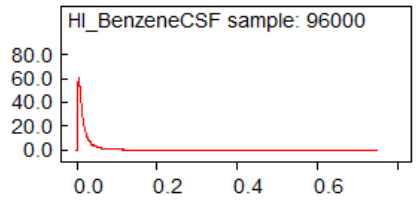


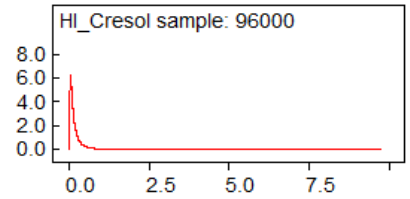
Prioritize for future validation

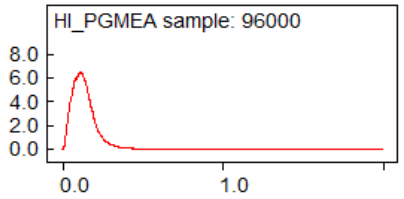
Risk Characterization

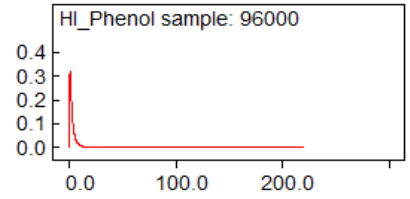
	HI	$HI_{95\%}$	sd
Benzene (at 2.19%)	11.08	34.75	14.6
Phenol	2.098	6.59	2.74
Cresol	0.286	0.9	0.37
PGMEA	0.13	0.26	0.0779
Xylene	0.0276	0.087	0.0358
Toluene	0.0102	0.032	0.013

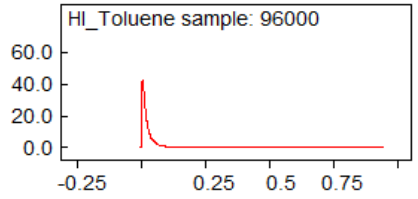


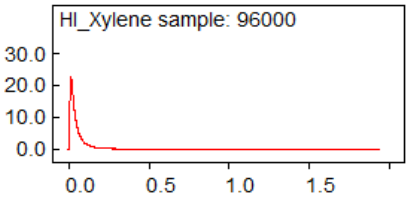




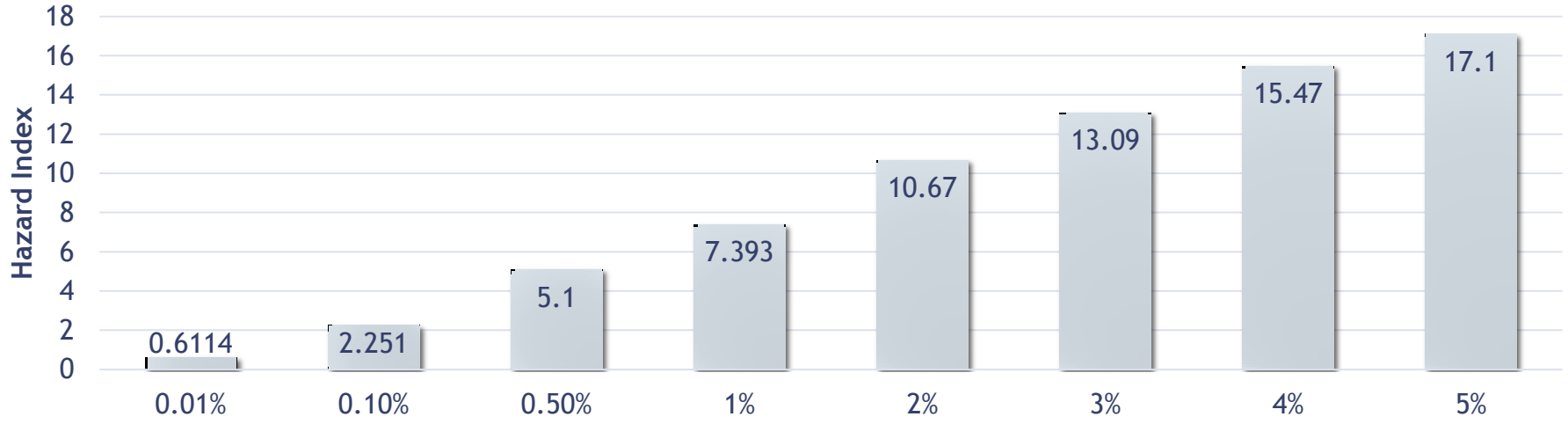


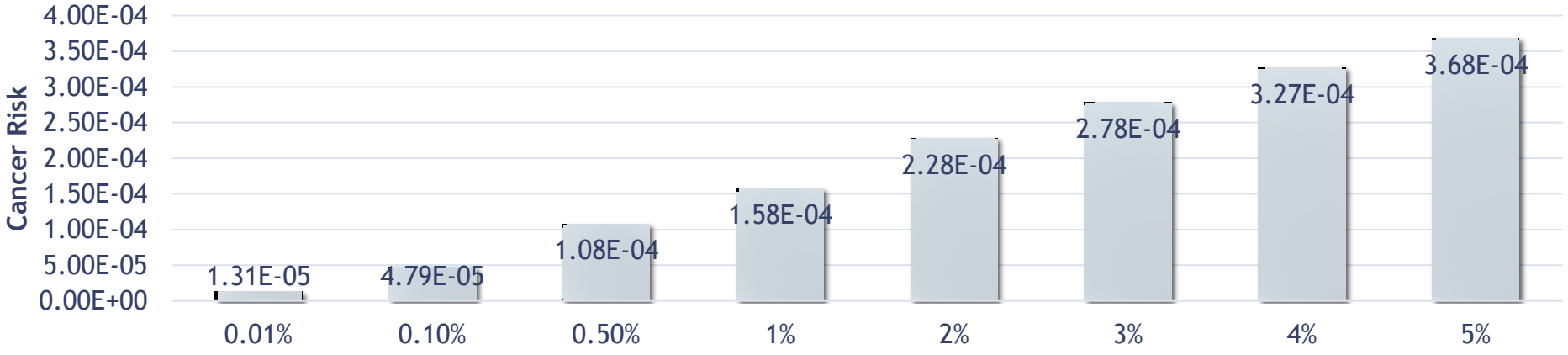






Risk at different assumptions on Benzene concentration





Conclusion and Suggestions

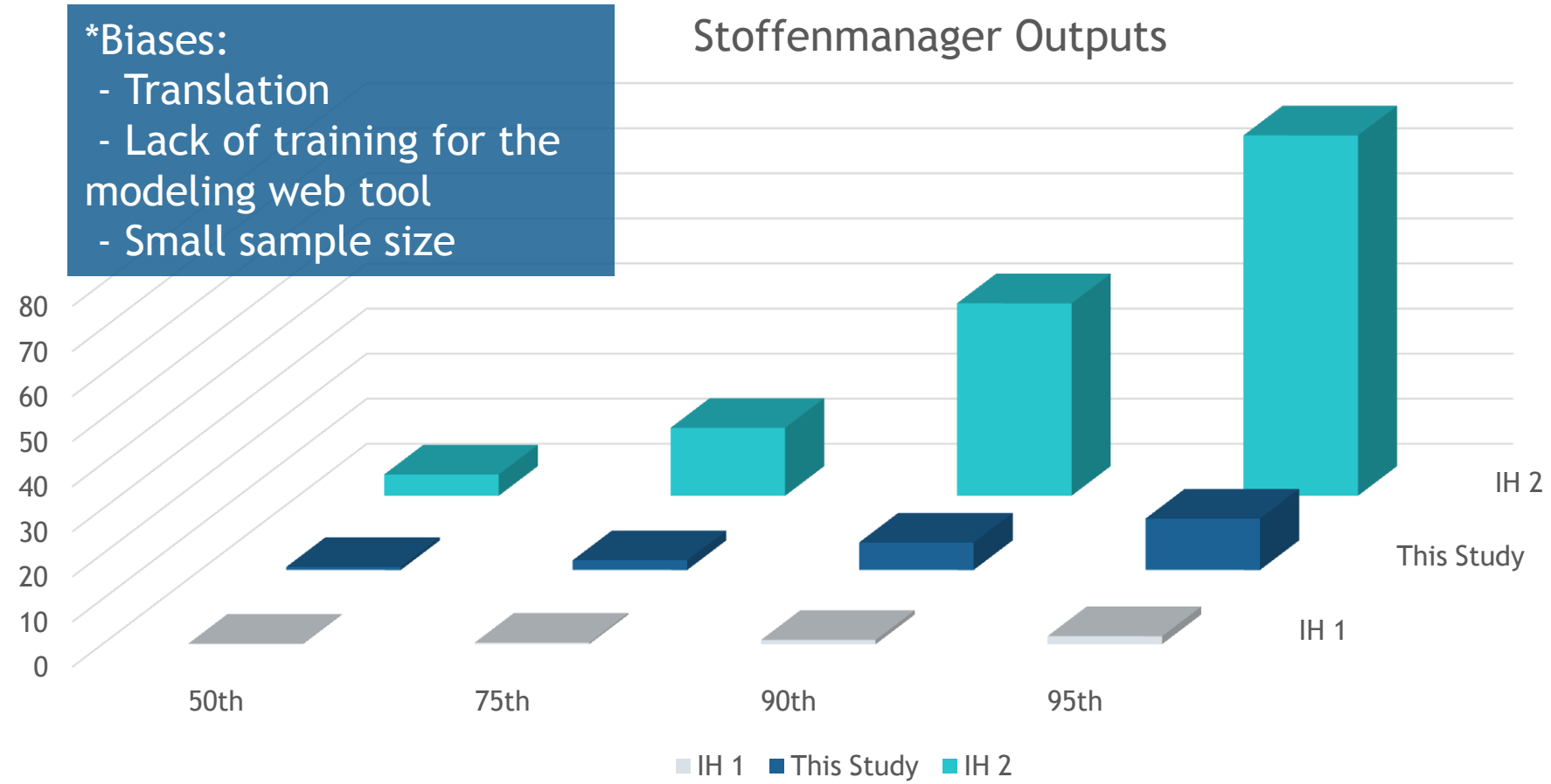
- This study demonstrate that health risk assessment on occupational hazards used could be pre-assessed in the design of process and equipment layout
- Benzene and phenol had unacceptable HIs (11.08 and 2.098, respectively), likely due to overestimated assumption of their concentrations in the photoresist.
- Sensitivity analysis suggested that the composition of benzene should be in the order of 0.01% in order for it to be acceptable

Thank you

Reliability of Stoffenmanager

Comparing Subjective Inputs

*Biases:
- Translation
- Lack of training for the modeling web tool
- Small sample size



Input differences between Industrial Hygienists

Working conditions	IH 1	IH 2
Activity in breathing zone	No	Yes
Multiple employees	No	Yes
Evaporation, drying or curing after activity	No	Yes
Activity	Handling of liquids where only small amounts of product may be released	Handling of liquids (using low pressure, but high speed) without creating a mist or spray/haze
Segregation of employee	The employee is situated in an open or closed cabin without specific ventilation system.	The employee does not work in a cabin.

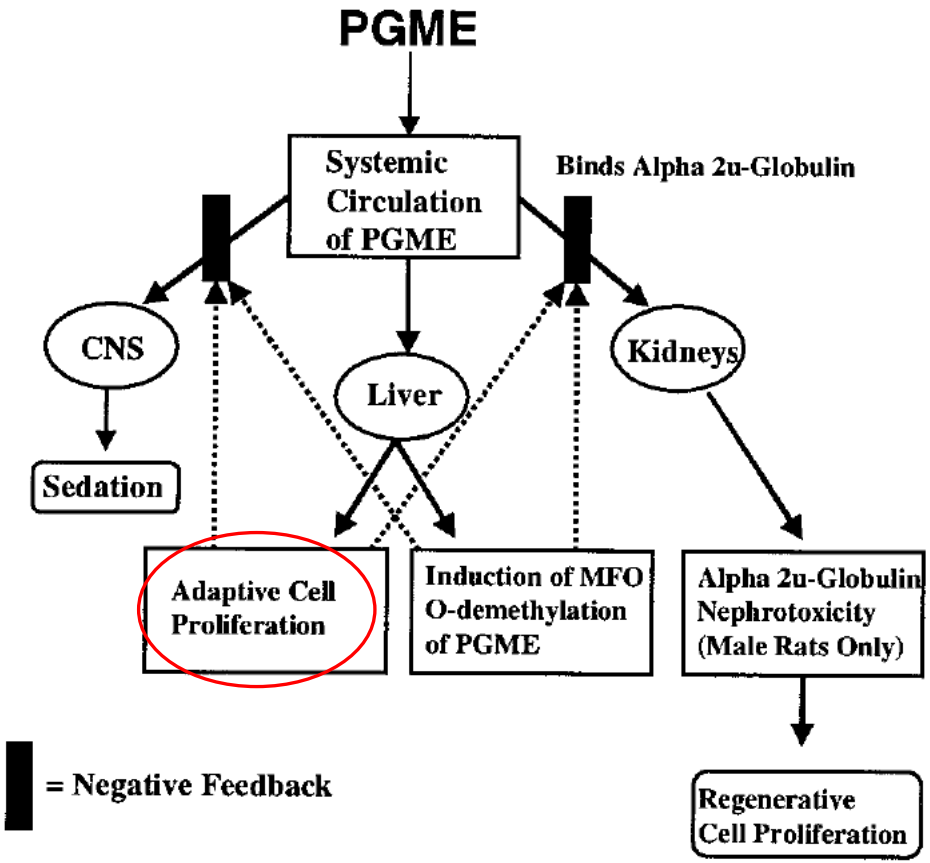
"Difficulties in interpretation and categorization" (Schinkel. Et al., 2014, Landberg and others 2015)

PGMEA

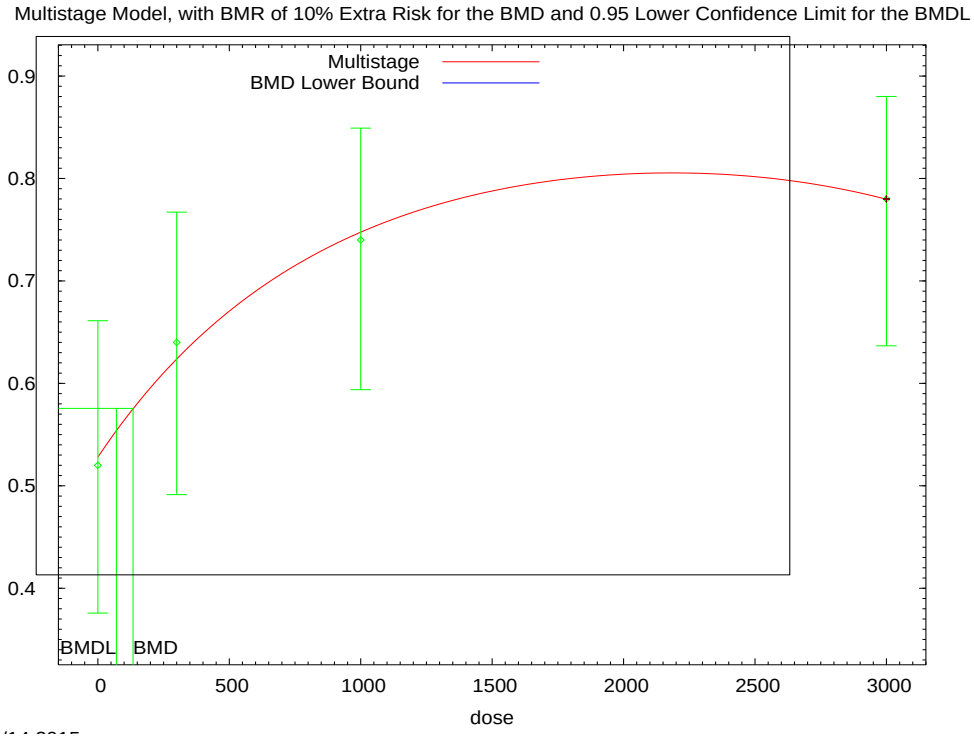
Quickly metabolizes to PGME due to hydrolysis

Critical Study	
Study Type	Chronic
Species	Rat
Target Effect	Eosinophilic Foci (Male)
0 ppm	26/50
300 ppm	32/50
1000 ppm	37/50
3000 ppm	39/50

(Spencer et al., 2002)



Model Name	AIC	P-value	Specified Effect	Risk Type	BMD	BMDL	Scaled residual for dose group near BMD
LogProbit	250.72	0.7021	0.1	Extra risk	35.3196		0.017
Multistage	250.657	0.7719	0.1	Extra risk	133.944	70.6316	-0.12
Multistage-Cancer	250.678	0.3526	0.1	Extra risk	401.63	231.841	0.409
Probit	251.079	0.2899	0.1	Extra risk	510.631	330.455	0.365
Weibull	250.678	0.3526	0.1	Extra risk	401.63	231.841	0.409
Quantal-Linear	250.678	0.3526	0.1	Extra risk	401.63	231.841	0.409



PGMEA
Equivalent continuous exposure:
BMDL x (6 hrs/24 hrs) x (5 day/7day)
= 12.6125 ppm

UF: Interspecies: 3
human variability: 10

RfC = 12.6125/30 = 0.42 ppm
= 1.55 mg/m^3

Phenol

Critical Study	
Study Type	Sub-Chronic
Species	Rat
Target Effect	Red Nasal Discharge
0 ppm	0/20
0.5 ppm	0/20
5 ppm	7/20
25 ppm	10/20

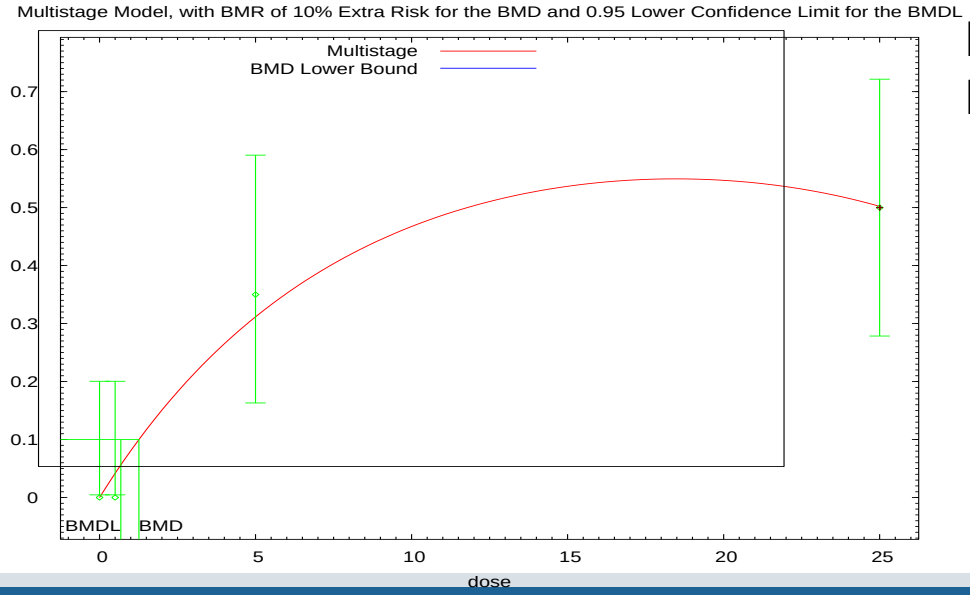
(Huntingdon, 1998)

Chronic studies that are **unsuitable** for Benchmark dose:

Species	Exposure (mg/m^3)	Duration	Response
Guinea pig, 12	100-200	6 wks	FEL – 5/12 dead
Rabbit, 6	100-200	13 wks	Pneumonia, heart inflammation, liver necrosis, kidney tubular degeneration
Rat, 12	100-200	74 days	No effect
Monkey, 10	0, 18.2	90 days	Liver and kidney
Rat, 50	0, 18.2	90 days	Liver and kidney
Mouse, 100	0, 18.2	90 days	Lung

(Deichmann et al., 1944, Sandage, 1961)

Model Name	AIC	Inputs+Estimates+Scaled Res.	P-value	Specified Effect	Risk Type	BMD	BMDL	Scaled residual for dose group near BMD
LogProbit	60.193	Array	0.3593	0.1	Extra risk	1.5696	0.3427	-0.79
Multistage	59.463	Array	0.6043	0.1	Extra risk	1.2619	0.68251	-0.933
Multistage-Cancer	61.039	Array	0.1195	0.1	Extra risk	2.7732	1.88832	2.093
Probit	70.537	Array	0.0028	0.1	Extra risk	7.5463	5.53476	2.841
Weibull	61.039	Array	0.1195	0.1	Extra risk	2.7732	1.88832	2.093
Quantal-Linear	61.039	Array	0.1195	0.1	Extra risk	2.7732	1.88832	2.093



Phenol

Equivalent continuous exposure:

BMDL x (6 hrs/24 hrs) x (5 day/7day)

UF: Interspecies: 10

human variability: 10

RfC = 1.22×10^{-3} ppm

= 4.69×10^{-3} mg/m^3

*IRIS did not publish a RfC

Provisional RfC: 0.006 mg/m^3

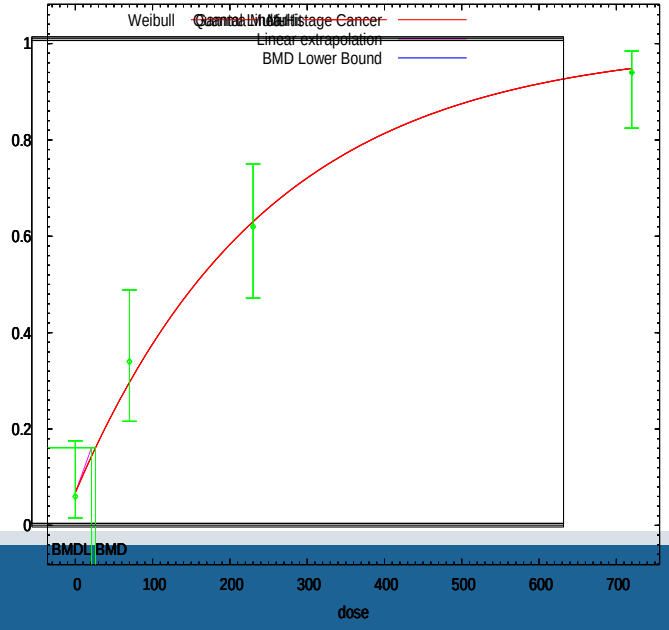
Cresol

Critical Study	
Study Type	Chronic (Oral)
Species	Male Rat
Target Effect	Respiratory epithelium, hyperplasia
0 ppm	3/50
1500 ppm	17/50
5000 ppm	31/50
15000 ppm	47/50

(Sanders et al., 2009)

- Lack of chronic inhalation
- Known to cause kidney toxicity, cell degenerations, and hyperplasia
- Metabolic pathway:
  - aromatic oxidation in the liver

Model Name	AIC	P-value	Specified Effect	Risk Type	BMD	BMDL	Scaled residual for dose group near BMD
Gamma	180.488	0.742	0.1	Extra risk	26.2081	21.0116	-0.23
Logistic	190.764	0.006	0.1	Extra risk	66.751	54.0267	1.137
LogLogistic	183.449	0.219	0.1	Extra risk	30.8996	13.9017	-0.093
LogProbit	183.046	0.287	0.1	Extra risk	32.3975	15.3316	-0.066
Multistage	182.259	0.549	0.1	Extra risk	23.8953	17.064	-0.111
Multistage-Cancer	180.488	0.742	0.1	Extra risk	26.2081	21.0116	-0.23
Probit	192.177	0.004	0.1	Extra risk	69.7484	57.9861	1.081
Weibull	180.488	0.742	0.1	Extra risk	26.2081	21.0116	-0.23
Quantal-Linear	180.488	0.742	0.1	Extra risk	26.2081	21.0116	-0.23



Cresol

BMCL = 21.01 x 60/20 / 0.5 = 126 mg/m^3

UF = 10 (species) x 10 (human variability)

RfC = 1.26 mg/m^3 =0.28 ppm

IRIS RfD: 0.05 mg/kg/d

*ACGIH-TLV: 5ppm

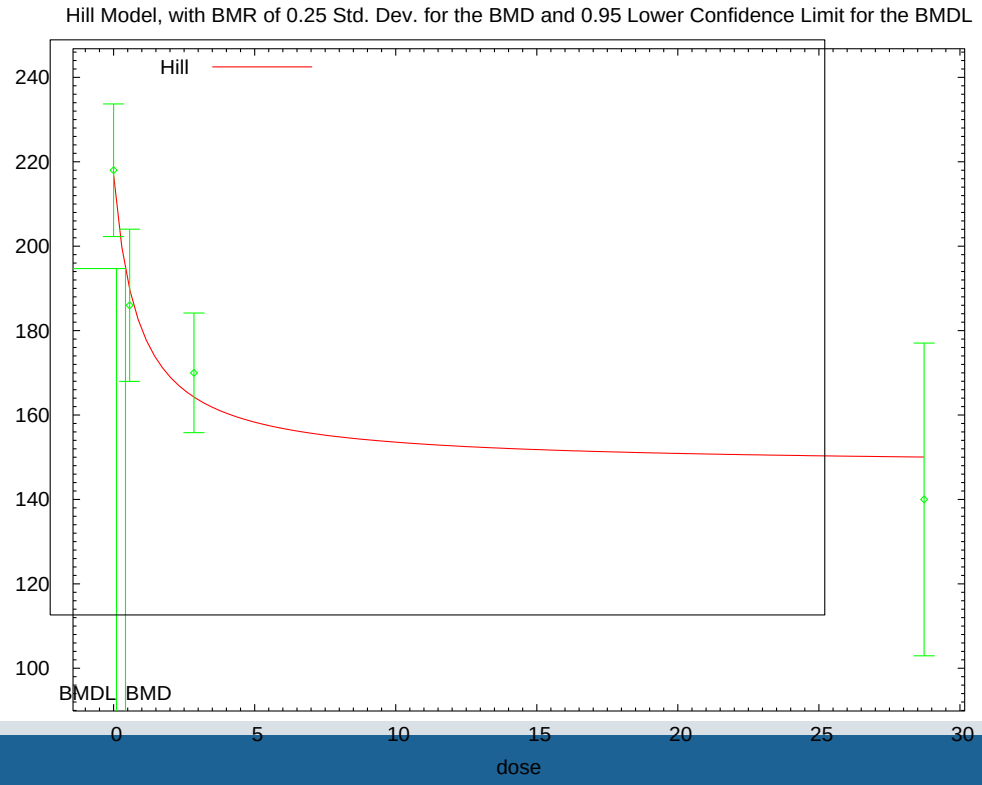
Benzene: Hematotoxicity

Subject category (*n*)*	Controls (140)	<1 ppm (109)	1 to <10 ppm (110)	≥10 ppm (31)	*P* for <1 ppm vs. controls†	P_{trend}, all subjects‡§
			Benzene exposure			
Benzene air level (ppm)‖	<0.04	0.57 (0.24)	2.85 (2.11)	28.73 (20.74)		
Benzene urine (μg/liter)¶	0.382 (1.24)	13.4 (18.3)	86.0(130)	847(1250)		
			Peripheral blood cell counts#			
White blood cells (WBC)**	6480 (1710)	5540 (1220)	5660 (1500)	4770 (892)	<0.0001	<0.0001
Granulocytes	4110 (1410)	3360 (948)	3480 (1170)	2790 (750)	<0.0001	<0.0001
Lymphocytes††	2130 (577)	1960 (541)	1960 (533)	1800 (392)	0.018	0.0014
$CD4^+$–T cells	742 (262)	635 (187)	623 (177)	576 (188)	0.003	0.019
$CD8^+$–T cells	553 (208)	543 (212)	564 (229)	549 (160)	0.75	0.97
$CD4^+/CD8^+$ ratio	1.46 (0.58)	1.26 (0.41)	1.22 (0.45)	1.09 (0.35)	0.015	0.024
B cells	218 (94)	186 (95)	170 (75)	140 (101)	0.003	0.0002
NK cells	586 (318)	558 (299)	566 (271)	415 (188)	0.56	0.0044
Monocytes	241 (92)	217 (97)	224 (93)	179 (74)	0.018	0.28
Platelets	230 (59.7) × 10^3	214 (48.8) × 10^3	200 (53.4) × 10^3	172 (44.8) × 10^3	0.023	0.0002
Hemoglobin (g/dl)	14.5 (1.6)	14.7 (1.5)	14.5 (1.7)	13.6 (1.6)	0.12	0.29

*The 28 subjects studied in both the first (2000) and second (2001) year of the study are categorized based on the exposure assessment in 2000. †Controls versus exposed <1 ppm, by linear regression on ln of each endpoint. ‡P_{trend} using ln air benzene as a continuous variable. All statistically significant endpoints were inversely associated with benzene exposure. §Comparison of subjects ≥10 ppm versus controls for endpoints without statistically significant trends: $CD8^+$–T cells, $P = 0.31$; monocytes, $P = 0.0006$; hemoglobin $P < 0.0001$. ‖Benzene air level is the arithmetic mean (±SD) of an average of two measurements per subject collected during the month before phlebotomy (9). This time period was chosen because granulocytes have relatively short half-lives in peripheral blood. ¶Urinary benzene (mean ± SD) and mean individual air levels of benzene were strongly correlated (Spearman $r = 0.88$, $P < 0.0001$). #Unadjusted mean (±SD) cells/μl blood. **Supplementary analyses are shown in the SOM Text. ††Absolute count.

Lan et al. (2004)

Model Name	Specified Effect	BMD	BMDL	p-value Test 1: Lack dose response?	p-value Test 2: Constant variance?	p-value Test 3: Good variance model?	p-value for fit: Does the model for the mean fit?	AIC	Scaled residual for dose group near BMD
Exponential2	0.25	8.26578	5.10297	< 0.0001	0.03773	0.03773	0.0009051	3915.279	-2.223
Exponential3	0.25	8.26578	5.10297	< 0.0001	0.03773	0.03773	0.0009051	3915.279	-2.223
Exponential4	0.25	0.384562	0.140936	< 0.0001	0.03773	0.03773	0.1105	3905.811	-0.2003
Exponential5	0.25	0.384562	0.140936	< 0.0001	0.03773	0.03773	0.1105	3905.811	-0.2003
Hill	0.25	0.421959	0.103932	<.0001	0.03773	0.03773	0.303	3904.32517	-0.46
Linear	0.25	10.1768	7.01271	<.0001	0.03773	0.03773	0.0006241	3916.02243	-2.32
Polynomial	0.25	0.374038	0.221726	<.0001	0.03773	0.03773	NA	3905.26405	-2.34E-06
Power	0.25	10.1768	7.01271	<.0001	0.03773	0.03773	0.0006241	3916.02243	-2.32



Benzene
Equivalent continuous exposure:
0.1 x 8/24 * 6/7
= 0.0286 ppm

UF: 10 (human variability)

RfC: 0.003 ppm = 9.6×10^{-3} mg/m^3

(Identical to ATSDR)

CSF: 2.22×10^{-6}
(Leukemia: Rinsky et al. 1981)

Toluene

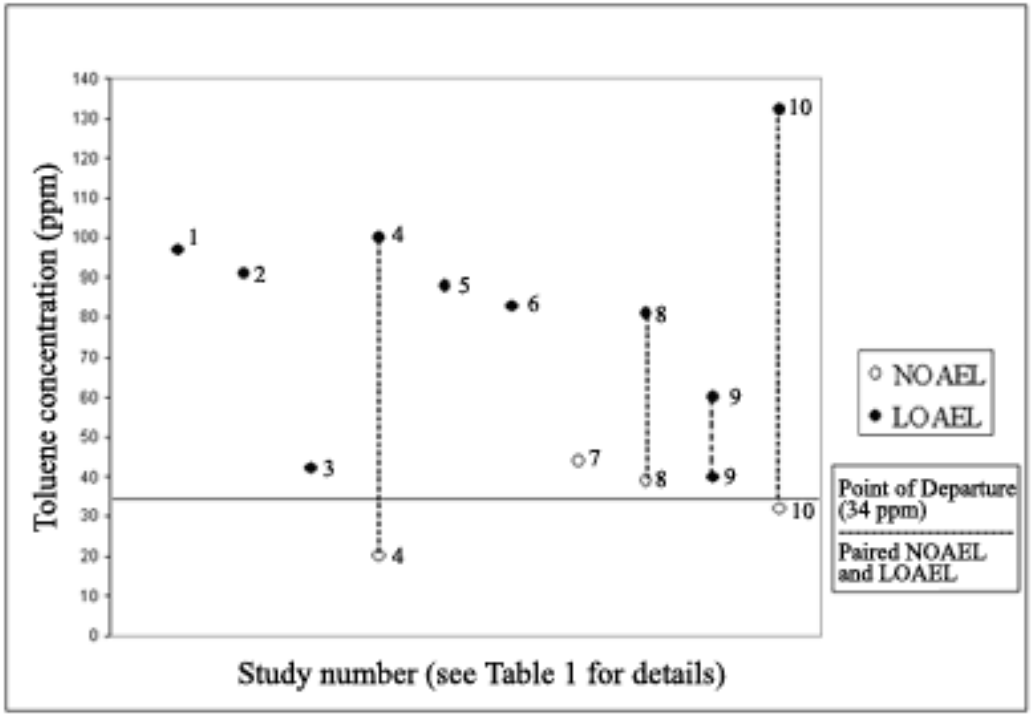
Neurotoxicity:

- Color vision impairment
- Cognitive performance decrease
- Difficulties in focusing

UF: 10 (human variability)

RfC: 3.4 ppm (5 mg/m^3)

(Revised 2005)



EPA 2005

Xylene

Critical Study	
Study Type	Chronic
Species	Rat
Target Effect	Rotar rod performance decrease
# per group	12
0 ppm	0%
50 ppm	8%
100 ppm	33%

Korsak, et al. 1994 (IRIS)

Neurotoxicity:

- Cognitive performance decrease

*Missing reports of standard deviation of the percentage

Xylene Korsak Study with Different standard deviations

Standard Deviation	BMDL (Power)
0.1	5.74 (AIC: -124.9)
0.2	7.355 (AIC: -75.0)
0.3	8.95 (AIC: -45.82)
0.4	10.286 (AIC: -25.105)
0.5	11.4463 (AIC: -9.04)

$BMDL_{ave}$ = 8.75546 ppm

UF:

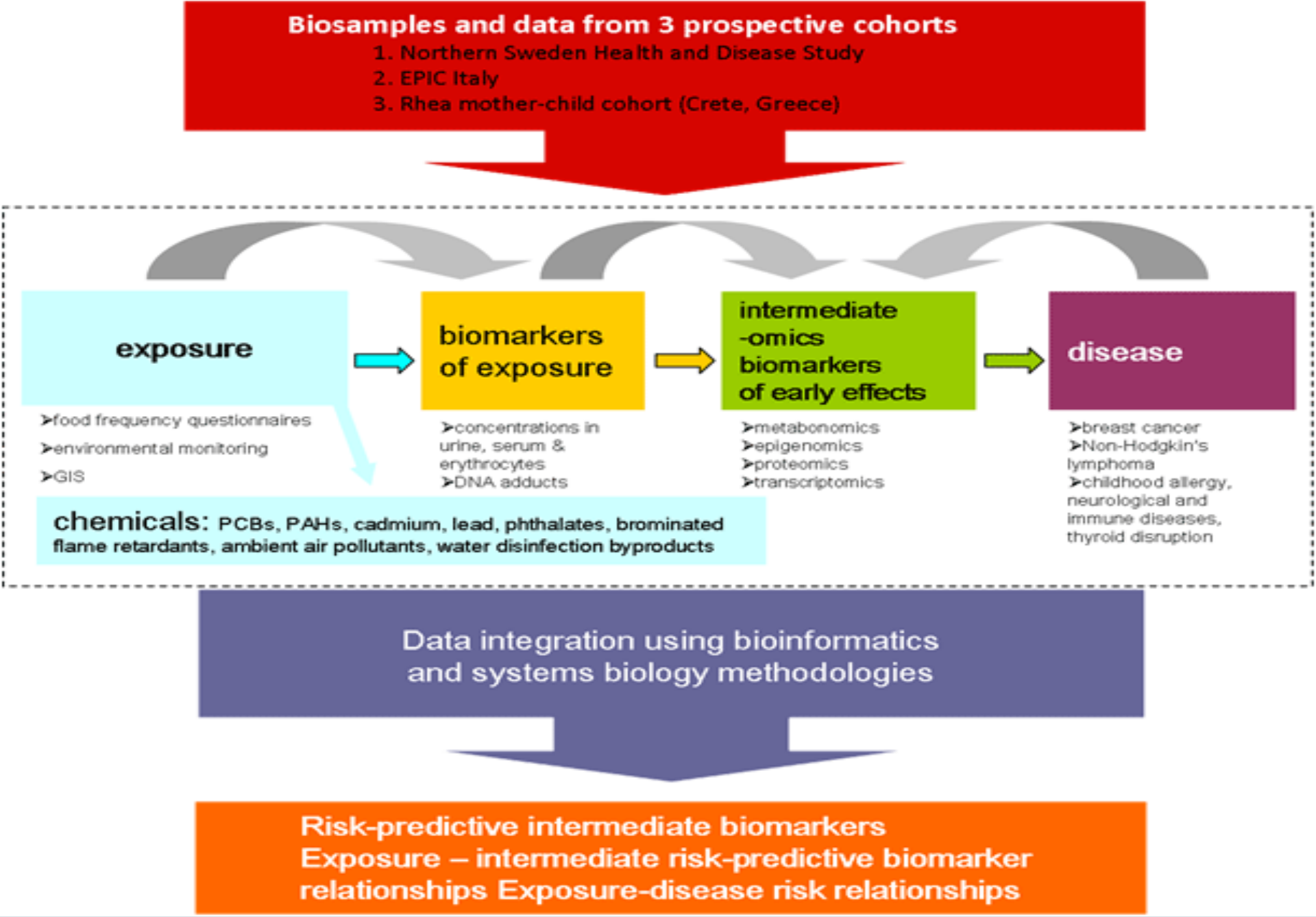
Interspecies (10)
Human variability (10)

RfC:

8.75546 x (6/24) x (5/7) / 100
$=1.56 \times 10^{-2}$ ppm
$= 6.78 \times 10^{-2}$ mg/m^3

RfC: 0.1 mg/m^3

Revised 2003


Biosamples and data from 3 prospective cohorts
1. Northern Sweden Health and Disease Study
2. EPIC Italy
3. Rhea mother-child cohort (Crete, Greece)
exposure
➢food frequency questionnaires
➢environmental monitoring
➢GIS
biomarkers of exposure
➢concentrations in urine, serum & erythrocytes
➢DNA adducts
intermediate -omics biomarkers of early effects
➢metabonomics
➢epigenomics
➢proteomics
➢transcriptomics
disease
➢breast cancer
➢Non-Hodgkin's lymphoma
➢childhood allergy, neurological and immune diseases, thyroid disruption
chemicals: PCBs, PAHs, cadmium, lead, phthalates, brominated flame retardants, ambient air pollutants, water disinfection byproducts
Data integration using bioinformatics and systems biology methodologies
Risk-predictive intermediate biomarkers
Exposure – intermediate risk-predictive biomarker relationships Exposure-disease risk relationships