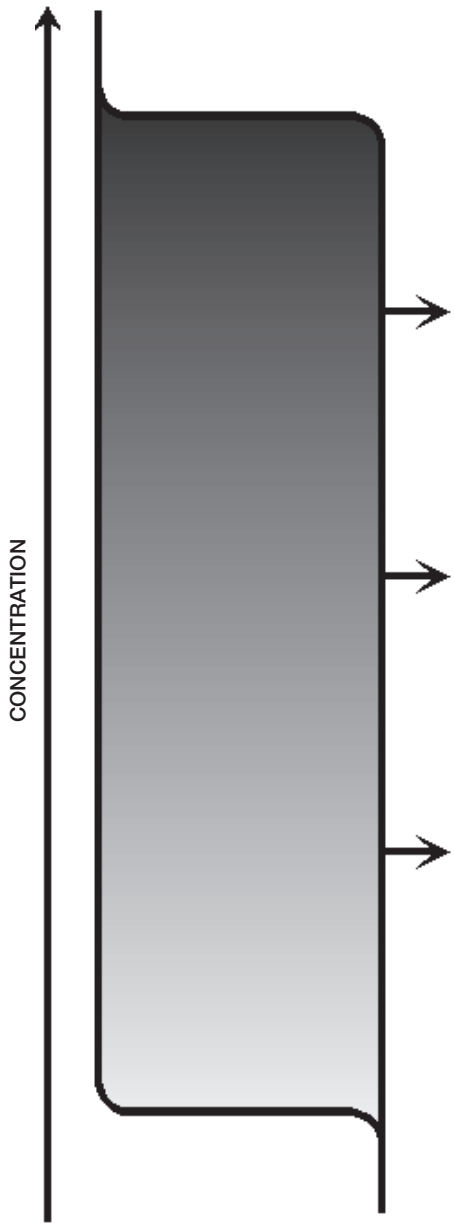
AIHA® Guideline Foundation

EMERGENCY RESPONSE PLANNING GUIDELINES®



Phenyl Isocyanate

ERPG–3: 1.2 ppm

The maximum airborne concentration below which nearly all individuals could be exposed for up to one hour without experiencing or developing life-threatening health effects.

ERPG–2: 0.4 ppm

The maximum airborne concentration below which nearly all individuals could be exposed for up to one hour without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action.

ERPG–1: 0.1 ppm

The maximum airborne concentration below which nearly all individuals could be exposed for up to one hour without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor.

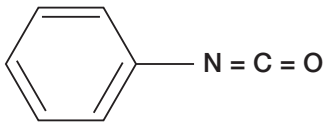
EMERGENCY RESPONSE PLANNING GUIDELINES®

Phenyl Isocyanate

ERPG–3: 1.2 ppm (6 mg/m³)
ERPG-2: 0.4 ppm (2 mg/m³)
ERPG-1: 0.1 ppm (0.5 mg/m³)

I. IDENTIFICATION[1]

Chemical Name:	Phenyl Isocyanate
Abbreviation:	PhI
Synonyms:	Phenyl carbamide, Carbanil; Mondur P, Isocyanatobenzene; Phenylcarbimide; Phenylic mustard oil; Phenylisocyanat (German); Isocianato de fenilo (Spanish); Isocyanate de phényle (French); Phenyl carbonimide.
CAS Number:	103-71-9
DOT Number:	UN2487
Molecular Formula:	C_7H_5NO
Structural Formula:	



II. CHEMICAL AND PHYSICAL PROPERTIES[2-5]

Physical State and Appearance:	Colorless liquid
Odor Description:	Pungent
Molecular Weight:	119.12
Conversion Factors:	(1013 hPa and 25°C): 1 mg/m³= 0.2 ppm 1 ppm = 4.9 mg/m³
Melting Point:	-31.3°C (-24.3°F)
Boiling Point:	165°C (329°F) at 760 mmHg
Vapor Pressure:	250 Pa at 20°C (68°F)
Vapor Saturation Concentration:	12219 mg/m³ at 20°C (68°F)
Specific Gravity:	1.095 g/cm³ at 20°C (68°F)
Vapor Density (Air = 1):	1.095
Flash Point (closed cup):	51°C (123.8°F)
Auto-ignition temperature:	300°C (572°F)
Stability and Reactivity:	Decomposes in water, alcohols, amines, and acid and alkaline moieties. Soluble in ethers, chloroform.
Solubility in Water:	not applicable (decomposition)

III. ANIMAL TOXICITY DATA

A. Acute Toxicity

The highly volatile aromatic monoisocyante PhI is a powerful lachrymator and respiratory tract irritant. Its vapor elicits a concentration-dependent upper respiratory tract sensory irritation, depression in ventilation in rodents, and exhibits a steep exposure-response relationship. The predominant site of damage within the respiratory tract occurs concentration-dependently with a typical *anterior-to-posterior* gradient of airway irritation. The intensity of PhI-induced tissue injury occurs at the site(s) of first contact in a concentration x time (Cxt)-dependent manner. Inhaled concentrations low enough to be retained in the bronchial airways cause a characteristic delayed-onset lethality as a result of progression of an *obliterating bronchiolar inflammation*. Exposure concentrations high enough to penetrate the alveoli cause an early-onset pattern of lethality as a result of acute lung edema.

1. *Oral Toxicity*[5]

   Rats: LD_{50} = 2500–2750 mg/kg[6]

   Rats: LD_{50} = 1044 mg/kg[7]

   Rats: LD_{50} = 172 mg/kg[7]

   Rats: LD_{50} = 887 mg/kg[8]

   Mice: LD_{50} = 196 mg/kg[9]

2. *Eye Irritation*

   Rabbits: ≈100 mg/eye = severe irritant/corrosive[5,6,10,11]

3. *Skin Irritation*

   Rabbits: ≈500 mg/4 hr = severe irritant[2], non irritant[7]

   Rabbits: ≈500 mg/24 hr = severe irritant/corrosive[5,11,12]

4. *Skin Toxicity*

   Rats: LD_{50} = approx. 5475 mg/kg[6]

   Rabbits (occlusive): LD_{50} > 2000 mg/kg-24 hr[7]

   Rabbits (occlusive): LD_{50} = 7130 mg/kg-24 hr[13]

5. *Inhalation Toxicity*

Rats: 1hr LC_{50} = 19-61* mg/m^3[14]

Rats: 4hr LC_{50} = 22 mg/m^3[15]

Mice: 30-min $RD_{50} \approx$ 5.9 mg/m^3[16]

Mice: 45-min $RD_{40*} \approx$ 12 mg/m^3[17]

Rats: 45-min $RD_{50} \approx$ 12 mg/m^3[17,18]

Guinea pigs: 45-min $RD_{40–50**} \approx$ 12 mg/m^3[17]

Acute inhalation nose-only studies using isocyanate functionality-specific derivatization methods for the analytical characterization of exposure atmospheres were given preference. Respiratory function measurements in mice, rats, and guinea pigs demonstrated an instant and concentration-dependent decrease in respiratory rate in all three species examined. The attainment of stable depression in ventilation was fastest in mice and rats and slower in guinea pigs, which matches the differences in spontaneous breathing activities of these species. In mice and rats exposed at ≈2 mg/m^3 a minimal depression of respiration was noticed.[17]

Fifty percent of the rats exposed nose-only to 5.4 mg/m^3 (1.08 ppm) for 4-hr elaborated first signs of respiratory tract irritation up to 4-day post-exposure (bradypnea, labored breathing patterns). The next lower concentration of 0.7 mg/m^3 (0.14 ppm) was tolerated without any effect. At lethal exposure concentrations, the rats elaborated signs of respiratory distress, cyanosis, stertorous respiration, hypothermia, and reduced motility. The median time required to attain fifty percent cumulative mortality occurred 8–9 days post exposure. At the 100% mortality range rats succumbed from Post-Exposure Days 1 to 18. Gross pathological findings of the respiratory tract were characterized by dark-red discolored lungs (atelectasis), viscous mucus in the lumina of bronchial airways (obliterating bronchiolitis), pleural exudates, and lung edema. Mortality data relative to the nominal and actual breathing zone concentrations are given in Table 1.[15]

Table 1: Mortality of directed-flow nose-only exposed rats to phenyl isocyanate for 4-hr and following by a post-exposure period of 4 weeks.[15]

Concentrations		Mortality [%] (5 rats/sex combined)
Nominal [mg/m^3]	Actual [mg/m^3] (ppm)	
2 (10)[a]	0.7 (0.14)	0
10 (50)	5.4 (1.08)	0
21 (100)	15.2 (3.04)	0
31 (150)	11.7[b] (2.34)	10
65 (310)	27.9 (5.58)	70
83 (400)	47.9 (9.58)	100
150 (730)	87.8 (17.56)	100

** Same exposure using two different analytical methods to define the actual concentration.*
*** RD_{50} stands for a reduction in the respiratory rate of 50% from the pre-exposure baseline respiratory rate (normalized to 100%).*

The exposure utilized a published directed-flow nose-only inhalation system using ≈20 L dry air/min for 20 exposure ports.[15,19] Atmospheres were generated using dry nitrogen passed through a gas bubbler. Nominal concentrations were calculated by the weight-loss of liquid PhI contained in the bubbler maintained at 20°C (digitally controlled water bath) during the 4-hour exposure period divided by the total throughput of chamber air. a) Values in brackets represent the weight loss in [mg] of the evaporating system during the 4-hour exposure period. b) Mortality and the intensity of clinical findings seem to better match the nominal rather than the actual concentration. This potentially erroneous analytical measurement had major impact on the calculation of slope and the non-lethal threshold concentration (LC_{01}).

In summary, 10.3 mg/m^3 (2.06 ppm) x 4 hr was calculated to be the LC_{01} based on probit analysis.[20] However, mortality did not occur in any sex at 15.2 mg/m^3. The hypothermic response was more pronounced at 11.7 mg/m^3 (2.34 ppm)as compared to that occurring at 15.2 mg/m^3 (3.04 ppm). Hence, the inconsistent relationship of the nominal to the actual concentration supports the conclusion that the actual concentration was expected to be higher than indicated by the analytical determination. Therefore, the highest empirically determined concentration without lethality (3.04 ppm) was given preference to the statistically derived LC_{01}.

B. Repeated Exposure

Young adult Wistar rats (10 rats/group/sex) were nose-only exposed in a technical optimization pilot study to actual breathing zone concentrations of 0, 0.12, 0.57, or 3.14 mg PhI/m^3 (isocyanate functionality-specific analytical derivatization method; concentrations equivalent to 0, 0.03, 0.1, or 0.7 ppm) for 6 hr/day on 5 consecutive days followed by a 3 week post-exposure period. Rats exposed to 3.14 mg/m^3 exhibited serous nasal discharge, which waned to normal by post-exposure day 8. Mortality did not occur in any group. Analyses of bronchoalveolar lavage fluid (BALF) yielded unremarkable changes.[21] Collectively, the results from this study 5x6-hour exposure study were qualitatively and quantitatively consistent with those of the single 4 hr-exposure study.

That 1-week pilot validation study was followed by a 4 week (6 hr/day, 5 days/week) nose-only inhalation study in young adult Wistar rats (10 rats/group/sex) to actual breathing zone concentrations of 0.35, 0.83, 2.8, and 10.1 mg PhI/m3 (isocyanate functionality-specific analytical derivatization method; concentrations equivalent to 0, 0.07, 0.17, 0.56 or 2.02 ppm). Up to 0.56 ppm clinical observations, body weights, organ weights, rectal temperature, reflexes, hematology, and clinical pathology were indistinguishable from the equally exposed air control. Histopathological changes were observed at 0.56 ppm and were characterized by Goblet cell hyperplasia in the nasal passages. At the next higher concentration at 2.02 ppm, the histological findings were essentially similar to those occurring after 2-week exposure (see below). Due to the similarity of findings and the greater depth on endpoints characterizing respiratory tract-related injury, the outcome of the 2-week study was taken as key study to derive an ERPG–2 equivalent scenario.[22]

Young adult Wistar rats (20 male rats/group) were nose-only exposed to actual breathing zone concentrations of 0 (air control), 1.0, 4.1, 7.2, or 10.4 mg PhI/m^3 (concentrations equivalent to 0, 0.2, 0.82, 1.44 or 2.1 ppm) for 6 hr/day on 5 consecutive days for 2 weeks followed by a 7 week post-exposure period. Exposure concentrations were selected to better distinguish concentration-dependent effects from Cxt-dependent outcomes. The time-adjusted 5.4 mg/m^3 (1.08 ppm) x 4 hr is equivalent to 3.6 mg/m^3 (0.72 ppm) x 6 hr. This equivalence was experimentally demonstrated by the 1-week pilot study (see above). Based on the Point of Departure (POD) of acute respiratory tract irritation, the selected concentration of 0.82 ppm was expected to elicit transitional to minimal respiratory effects. The next higher concentrations were estimated from the time- adjusted 15.2 mg/m^3 (3.04 ppm) x 4 hr acute exposure level, resulting in a 10.1 mg/m^3 (2.03 ppm) x 6 hr equivalent as the non-lethal threshold concentration following single exposure. However, differences in inhaled dose have to be accounted for since the lethality-based threshold is derived from data exceeding markedly the RD_{50} of rats. This means, at concentration x time relationships within the range of 1.44 and 2.1 ppm x 6 hr, an over-proportionally higher ventilation (and inhaled dose) can be expected. Hence, any recurrent exposure to the acute non-lethal threshold Cxt was expected initiate/propagate a typical "acute-on-chronic" aggravation of the acute airway inflammation. While aggravation of acute sensory (concentration-dependent) airway irritation (in the absence of any significant Cxt-dependent inflammation) was not expected to occur at 0.2 and 0.82 ppm, the recurrent aggravation of airway inflammation was expected to cause lethality delayed in onset (due to the progression of obliterating bronchiolitis). This anticipated outcome is consistent with the Mode of Action of this monoisocyanate. This anticipated acute Mode of Action was evaluated further by pulmonary function tests, blood gas and BALF analyses shortly after the exposure and towards the end of the ≈2-months post-exposure periods. These time points allow for a better appreciation of direct irritation-related effects and the tissue responses occurring secondary to the acute lung injury.

Major findings were characterized by decreased body weights, hypoactivity, hypothermia, signs of respiratory tract irritation, typical delayed onset of mortality, and changes in organ weights (spleen and thymus weight were significantly decreased, lung weights were significantly increased) at 1.44 and 2.1 ppm. At terminal sacrifice lung weights were still elevated. No statistically significant and concentration-dependent changes to the organ-to-brain weight ratios of adrenals, heart, and testes were observed. Lung function tests demonstrated decreased forced expiratory flow rates and quasistatic lung compliance (loss of elastic recoil due to lung edema). Arterial blood gases showed an arterial hypoxemia and changes consistent with a pronounced mismatch of the ventilation : perfusion relationship. At these lethal exposure levels evidence of hemoconcentration existed. Delayed-onset of mortality appeared to be associated with respiratory acidosis, hypoxemia, and marked shifts of peripheral blood into the lungs as a typical sequelae of acute lung injury.[23] Analyses of BALF complemented the results of functional endpoints. Changes suggestive of airway injury

and inflammation included γ-glutamyltransferase, protein, and sialic acid. Histopathological findings provided evidence of increased secretory cell activity with increased Goblet cell hyperplasia at concentrations of 0.82 ppm and above. Additional findings were observed in rats exposed at 1.44 ppm and above, such as intraluminal inflammation of airways, hypertrophy of bronchial smooth muscle, epithelial desquamation, and an eosinophilic airway inflammation.[18]

In summary, with the exception of Goblet cell hyperplasia in the nasal, paranasal regions, and main bronchi of rats exposed at 0.82 ppm, the incidences of histopathologic lesions in rats of the 0.2 and 0.82 ppm exposure groups were not significantly different from the control. Rats in these groups were free of clinical signs. Findings in the two highest exposure groups were indicative of significant airway injury and decrements in pulmonary function consistent with the clinical signs of respiratory tract irritation. Most of the apparent systemic effects observed in the 1.44 and 2.08 ppm groups (organ weights, blood gas changes) seem to be causally linked to reflexively-induced bradypnea, hypothermia, hypoxemia, and dysregulated cardiopulmonary function at lethal exposure levels. Reflexively-induced bradypnea and related cardiopulmonary changes, including hypothermia, are sequelae of rodent-specific nociceptive responses that have limited relevance for humans. Organs susceptible to recurrent sensory irritation-related distress include the thymus. Lung injury can further be exacerbated by pulmonary hypoxic vasoconstriction as occurring during life-threatening pulmonary edema. The associated decrease in heart rate (cardiac output) and systemic vasoconstriction re-distributes the plasma volume into the lung, which amplifies the acute edema and anoxic anoxia in a hemodynamic state of accompanying hemoconcentration and raising blood viscosity.[23] All of these factors seriously impede further gas exchange and causes an imbalance of the fluid-dynamics of the lung. As far as systemic changes were observed, they appear to be causally related to the acute-on-chronic lung injury severe enough to cause lethality. These findings are typical for lethal, irritation-related acute lung injury[23] and cannot be taken as evidence of systemic bioavailability of inhaled PhI.

C. Reproductive/Developmental Toxicity

Pregnant Halle-AB-Jena and Halle-DBA mice were administered 9.8 mg/kg PhI by gavage on Gestation Days 4, 7, 11, and 15. Animals were sacrificed on Gestation Day 18. The corpora lutea and dead implantations were recorded. There was no evidence of any PhI-induced embryotoxicity.[9]

D. Genotoxicity

There was no significant evidence of mutagenic effects in Salmonella/microsome, E. coli Sd-4-73, and Streptomyces aureofaciens tests.[24-29] Results of a mouse cytogenicity test did not reveal evidence of any chromosomal aberrations following a single 5 or 10 mg/kg dose of PhI by gavage and bone marrow analysis 1- and 2-days post-application.[9] Results from a mouse micronucleus test following a single i.p. injection of 30 mg/kg phenyl isocyanate and analysis of bone marrow 1-, 2-, and 3-days post-injection, did not reveal evidence of any clastogenic effect. Dosed animals showed apathy, ungroomed hair-coat, spasms, irregular breathing, and diarrhea. Mortality occurred in 1 of 40 animals.[30]

E. Sensitization

A mouse ear-swelling test (MEST) with phenyl isocyanate was performed using non-occlusive application of 100 µL of an acetone solution containing 0.03 to 250 µg PhI onto the abdomen of six BALB/c mice. Four days later, 20 µL of a non-irritant 0.1 % solution containing 20 µg PhI was applied to each side of the right ear. The left ear was treated for control purposes only with acetone. Triplicate measurements of ear thickness were made 24 hr following the challenge using a spring-loaded micrometer. The ear thickness increase was calculated as the difference in thickness between the mean pre- and post-challenge measurements. The SD_{50}, which predicts to sensitize 50% of the mice, was derived from probit analysis of MEST data. The SD_{50} was 0.04 µmol (0.005 mg)/kg body. To achieve the same outcome with the diisocyanates hexamethylene or toluene diisocyanate, the doses required were markedly highly 0.5 and 30 µmol (0.06 and 3.6 mg)/kg body weight, respectively.[31]

Groups of eight BALB/c mice were treated on each shaved flank with 50 µL of a 1 % solution of phenyl isocyanate or toluene diisocyanate in acetone/olive oil (4:1) (total dose 1 mg). After 14 days the total IgE was not increased in either group relative to the level in the control animals. On the other hand, the animals treated with phenyl isocyanate were found to have higher IgG and IgG_1 titers on average than the animals treated with toluene diisocyanate.[31]

In a modified maximization test, dose-dependent sensitization was demonstrated. Groups of Hartley guinea pigs received intradermally PhI in ethanol/propylene glycol (20:80) (200 or 2000 µg/mL) and epicutaneously with 2000 µg/mL in the same vehicle for induction. The results on non-occlusive provocation with 200 and 2000 µg/mL in acetone are summarized in Table 2.[32]

Table 2. Summary of findings using a modified Guinea Pig Maximization Assay[32]

Concentration [ppm-vehicle]	Concentration [ppm-vehicle]	Concentration [ppm-vehicle]	SR	MR
0	0	0, 2, 20, 200, 2,000	0/5[a]	0
200	2,000	0, 2, 20 200 2,000	0/5[a] 3/5 5/5	0 0.6 2.4
2,000	2,000	0, 2, 20 200 2,000	0/5[a] 3/5 4/5	0 0.2 1.4

a) Five animals/group each; SR: sensitization rate – positive number of animals / total number of animals; MR: mean response – summation of numerical scoring / total number of animals.

In an exploratory study focusing Pirbright-White-Dunkin-Hartley guinea pigs were intradermally sensitized to phenyl isocyanate with 100 µL of a 0.5 % peanut oil on each flank on 3 alternate days. The control received the vehicle under otherwise identical conditions. Another group of 8 animals was exposed by inhalation for induction purposes to phenyl isocyanate in concentrations of 48 mg/m^3 for 15 minutes. After 2-weeks, the animals were challenged with PhI at 4.2 mg/m^3 for 30 minutes. The respiration rate was changed in 4/8 animals sensitized by inhalation exposure, in 1/8 animals sensitized intradermally, and in 1/8 control animals; sensitized animals showed more rigorous responses upon challenge than controls. Acetylcholine-induced unspecific airway was indistinguishable amongst groups. One week thereafter the guinea pigs were challenged with PhI–guinea pig albumin conjugate at 33 mg/m^3 for 30 minutes with no changes in lung function parameters in the control or inhalation-sensitized animals. Conversely, animals sensitized intradermally and challenged with the conjugate displayed marked airway reactions in 6/7 animals. Intradermally sensitized guinea pigs showed significantly higher titers for anti-phenyl isocyanate IgG_1 antibodies.[33,34]

F. Metabolism/Pharmacokinetics

No data available

IV. HUMAN EXPERIENCE

A. Sensitization

In the literature, there are no clinical reports of symptoms in persons exposed to phenyl isocyanate. This is, however, probably because sufficient skin extended contact with PhI is unlikely to occur due to its volatility. In several employees with respiratory symptoms who were exposed to isocyanates, also specific IgE against phenyl isocyanate–HSA conjugate was detected. Whether this sensitization was the result of the contamination of other isocyanates with PhI or of cross-reactions was not investigated. Allergenic airway effects were identified in an exploratory study with guinea pigs. Within the DFG notification scheme of sensitizers to judge positive results from animal studies, PhI was categorized as a potential skin and respiratory sensitizer.[35] Within the EU classification system PhI was not categorized as respiratory sensitizer.[36] Additional qualitative information on human data is available online.[2,37]

V. MECHANISM OF TOXICITY, TIME ADJUSTMENT, AND UNCERTAINTY FACTORS

Published evidence from other volatile mono- or diisocyanates was not considered in this appraisal, since the depth of penetration and localized injury of each individual isocyanate is highly dependent on its reactivity towards nucleophiles present in and the partition/solubility of the vapor phase to/in the fluids lining the airways of the lung. The concentration and types of constitutively present nucleophiles change from one location of the respiratory tract to another that attributes to the site-of-retention specific toxicity of inhaled volatile isocyanates. Based thereupon, injury may be confined to the airways, the alveoli, or to both.[38,39] As alluded to above, the manifestation of toxicity may vary conspicuously amongst isocyanates depending on the site of initial retention and response to injury.

The duration relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$. In the absence of an empirically derived exponent (n), temporal scaling from the experimental durations of the respective PODs to ERPG-specific durations is generally be performed using $n = 3$ when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points using the $C^n \times t = k$ equation.[40,41] However, as exemplified for the somewhat similar volatile and reactive monoisocyanate n-butyl isocyanate, the respiratory minute volume can substantially be depressed in rats at higher (and shorter) exposure concentrations resulting in a marked under-appreciation of the inhaled dose. This is caused by a rodent-specific reflexively-induced bradypnea. The associated changes in cardiopulmonary function are often misconstrued as systemic effects.[23,42] Accounting for this circumstance, the extrapolation from longer exposure periods at lower concentrations would elicit less reflex bradypnea. Therefore, based on the recommendation given elsewhere[43], n = 1 was used when extrapolating longer to shorter time points.

No mortality occurred at 15.2 mg/m³ (3.04 ppm) x 4h in the single exposure study in rats. The hypothermic response was more pronounced at 11.7 mg/m³ (2.34 ppm) as compared to 15.2 mg/m³ (3.04 ppm). Therefore, the LC_{01} of 3.04 ppm was given preference to any statistically derived threshold. Time extrapolation to 1 hr is most adequate following Haber's Rule with C^n x t = const. and n = 1 as demonstrated elsewhere for a somewhat similar monoisocyanate.[42] Any shorter duration of exposure with higher concentrations would have caused a higher depression in ventilation resulting in a proportionally higher tolerance. Accordingly, 12 ppm x 1 hr is considered to be the appropriately time-adjusted non-lethal threshold concentration equivalent to 3 ppm x 4 hr. Based on respiratory function measurements and observation of animals, ≈1 mg/m³ is considered to be the threshold concentration for eliciting an immediate-onset concentration-dependent *sensory* irritation. The threshold was similar both after single and repeated inhalation exposure. The time-independence of this threshold was further substantiated in the 2-week repeated exposure study using biochemical, functional, and histopathological endpoints for defining the no-observed-adverse effect level. Following repeated exposure to 0.82 ppm x 6 hr rats elaborated histopathological evidence typical of adaption rather than injury. Therefore, this concentration is taken as POD to protect for irreversible effects to occur following a single exposure. Time-adjusted, 4.8 ppm x 1 hr was considered to be the appropriately threshold level for this intrinsically reversible endpoint.

The intraspecies uncertainty was addressed by a factor of 3. The interspecies uncertainty was also addressed by an additional factor of 3. The outcome of the 2-week 6 hr/day repeated exposure study with multiple endpoints to probe lung injury biochemically, physiologically, and histopathologically supports the approach taken. The interspecies uncertainty factor of 3 also adjusts for the reflexively-induced depression in ventilation, which cannot be translated to humans.

VI. CURRENT OCCUPATIONAL EXPOSURE GUIDELINES

A. One-hour AEGLs for phenyl isocyanate published in 2013 by the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee)[44] are

AEGL–3: 0.029 ppm

AEGL–2: 0.0096 ppm

AEGL–1: n/a

Notably there are remarkable differences in the final AEGL values and the proposed ERPG values. In the preceeding Interim AEGL document as of 2009[45], the respective interim values were for the AEGL–1, –2 and –3 for 1 hour 0.02, 0.15, and 0.24 ppm, respectively. These values were lowered for the final value published in 2013[44] based on the following rationale: The AEGL–3 based 4-h BMCL05 value of 1.64 ppm was calculated from the rat lethality data used which also was key study in this appraisal. This POD is supported by data from a repeated 2-week nose-only inhalation study at 5 x 6-h/week exposures to PhI, in which 2.1 ppm was not lethal to 20 male rats exposed for 2 weeks, including a 2 months post-exposure period (the same key study was used in this appraisal). Interspecies and intraspecies uncertainty factors of 3 and 10, respectively, were applied. An interspecies uncertainty factor of 3 was considered appropriate on the basis of mortality data on the related compound methyl isocyanate that indicated limited species differences; about a two-fold difference in 6-h LC_{50}s for rats, mice, and guinea pigs was found. A factor of 3 was also consistent with that used for deriving AEGL values for methyl isocyanate. A factor of 10 was applied to account for intraspecies variability, and was also consistent with the factor applied in the derivation of AEGL–3 values for methyl isocyanate. Finally, a modifying factor of 3 was applied to account for potential developmental toxicity of PhI on the basis of data on methyl isocyanate. Time scaling was performed using the equation $C^n \times t = k$, with default values of n =1 for extrapolating to longer durations and n = 3 for extrapolating to shorter durations. AEGL–2 values were calculated on the basis of the available animal data, the most relevant POD was considered to be the estimated threshold for respiratory-tract injury. In the same acute inhalation key study as used in this appraisal, 0.8 ppm would be a no-effect level for AEGL–2 severity effects. AEGL–2 values could be calculated by applying a total uncertainty factor of 30 (3 for interspecies differences and 10 for intraspecies variability), applying a modifying factor of 3 (to account for potential developmental toxicity of *n*-butyl isocyanate and on the basis of data for the related compound methyl isocyanate), and performing time scaling with the equation $C^n \times t = k$ (using default values of n = 3 for extrapolation to shorter durations and n = 1 for extrapolation to longer durations).

Remarks: In the presence of state-of-the-art and substance-specific information from harmonized testing guideline compliant GLP-studies directed towards a better understanding of the PhI-induced respiratory tract toxicity cannot be replaced by non-GLP exploratory studies with methyl or other aliphatic isocyanates originating from a more science-based work-up of the Bhopal accident in India 1984. Current regulatory testing guidelines give preference to the rat as species of choice. These guidelines would not support using additional species in the absence of any robust justification due to animal welfare reasons. The applied

time-extrapolations are not state-of-the-art based on the explanations given in the previous section. The interrelationship of concentration-dependent 'sensory irritation' and concentration x time (= dose)-dependent 'respiratory tract irritation and inflammation' was meticulously addressed in the referenced inhalation studies but not adequately considered in the derivation of the AEGLs (for details see preceding section). The chemical reactivity of PhI precludes any systemic bioavailability of PhI. Adversity is solely contingent upon a local, initial 'site-of-retention'-specific mode of action. However, sequelae of apparent 'systemic toxicity' may occur as a result of rodent-specific, generic nociceptive responses to reflex-bradypnea that cannot be translated to humans.[46,47] Acute-on-chronic effects (recurrent-exposure of animals with aggravated acute inflammation at the portal of entry) does not occur in 'once in a lifetime' emergency scenarios the AEGL-values are actually derived for.

An occupational exposure Level Limit Value of 0.005 ppm and a 5–13 minute Ceiling Value of 0.01 ppm is listed by the Swedish Work Environment Authority.[48] The DFG-MAK Commission Germany classified phenyl isocyanate as skin and respiratory sensitizer.[35] BAuA (Federal Institute for Occupational Safety and Health; Committee on Hazardous Substances) published an allowable workplace level for phenyl isocyanate of 0.01 ppm (0.05 mg/m³).[49]

VII. RECOMMENDED ERPGS AND RATIONALES

A. ERPG–3: 1.2 ppm (6 mg/m³)

1.2 ppm is the maximum concentration to which nearly all individuals could be exposed to PhI for up to one hour without lifethreatening effects. This is based on available acute inhalation data in which exposures of 3.1 ppm for 4 hr were nonlethal in male and female rats.[15] The 1 hr adjusted concentration of 12.4 ppm was subjected to a total intra-/interspecies factor of 10.

B. ERPG–2: 0.4 ppm (2 mg/m³)

0.4 ppm of PhI is the maximum airborne concentration below which nearly all individuals could be exposed for up to 1 hr without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action. A repeated 2-week inhalation study in rats to 0.82 ppm x 6 hr/day is taken as point of departure to protect for irreversible effects to occur following a single exposure.[18] With regard to sensory irritation, any impairment of the ability to take protective action is not expected to occur at 0.4 ppm since an exposure level of 0.82 ppm was tolerated repetitively without clinical evidence of mucus membrane irritation. The time-adjusted exposure equivalent of 4.9 ppm x 1 hr is considered to be the highest concentration to fulfil the criteria applicable. The 1 hr-adjusted concentration of 5 ppm was subjected to a total intra-/interspecies factor of 10. Due to the steep dose-response curve for lethality, a factor of 3 to the ERPG–3 was observed.

C. ERPG–1: 0.1 ppm (0.5 mg/m³)

0.1 ppm is the highest concentration to which nearly all individuals could be exposed for 1 hour to phenyl isocyanate without experiencing or developing effects more serious than mild irritation. This level is slightly lower than the no-observed-adverse level following repeated exposure of rats (0.2 ppm). Functional measurements in rats and mice demonstrated very mild sensory irritation to occur in the range of 0.2 to 0.4 ppm (RD_{50}: ≈2.7 ppm). Sensory irritation is triggered from receptors of the upper respiratory tract by direct exposure. An interspecies uncertainty factor of 3 (for differences in dynamics) was used to adjust sensory irritation from rodents to humans. The RD_{50} concentration was suggested to be intolerable in humans; however, 1/30 of the RD_{50} is commonly considered to be tolerable for occupational exposure patterns.[49] Hence, the approach taken is concordant with published evidence.

VIII. HISTORY OF PHENYL ISOCYANATE

First published in 2016: ERPG–1: 0.1 ppm; ERPG–2: 0.4 ppm, ERPG–3: 1.2 ppm.

IX. REFERENCES

1. **BG Chemie (Berufsgenossenschaft der chemischen Industrie):** *Phenylisocyanat, Toxikologische Bewertung No. 198*, BG Chemie, Heidelberg (1997). Available at: https://www.bgrci.de/fileadmin/BGRCI/Downloads/DL_Praevention/Fachwissen/Gefahrstoffe/toxikologische_bewertungen/Bewertungen/ToxBew198-K.pdf) [accessed October 4, 2015].
2. **HSDB (Hazardous Substances Data Bank).** Phenyl Isocyanate. CAS No. 103-71-9. TOXNET, Specialized Information Services, U.S. Library of Medicine, Bethesda, MD (2012). Available at: http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB [accessed October 4, 2015].
3. **Budavari, S., M.J. O'Neil, A. Smith, P.E. Heckelman, and J.F. Kennedy (eds.):** Phenyl isocyanate. The Merck Index. 11th edition. Whitehouse, NJ: Merck and Co., 1996.

4. **IPCS (International Programme on Chemical Safety):** Phenyl Isocyanate. International Chemical Safety Card ICSC: 1131 (2002). Available at: http://www.inchem.org/documents/icsc/icsc/eics1131.htm [accessed October 4, 2015].

5. **EU, 2012:** European Chemicals Bureau; IUCLID Dataset, phenyl isocyanate (103-71-9) (online edition). Available from, as of March 16, 2012: http://apps.echa.europa.eu/registered/data/dossiers/DISS-d019684e-2bb0-2114-e044-00144f67d249/AGGR-f56a34e8-329f-4f8c-9f31-a9775550d918_DISS-d019684e-2bb0-2114-e044-00144f67d249.html [accessed October 4, 2015].

6. **Mihail, F. and J. Thyssen:** Phenylisocyanat: Untersuchungen zur Gewerbetoxikologie. Report No. 9694. Bayer AG Institut für Toxikologie, Wuppertal-Elberfeld, Germany. January 20, 1981 (unpublished).

7. **Lamb, D.W. and C.S. Matzkanin:** Mobay Chemical Corporation/ Chemagro Agricultural Division, unpublished report no. 44762 as of 01.07.1975 (cited in BAuA, 2006; available at: http://www.baua.de/de/ Themen-von-A-Z/Gefahrstoffe/TRGS/pdf/900/900-phenylisocyanat.pdf).

8. **Löser, E.:** Bayer AG, unveröffentlichter Bericht vom 17.10.1980(cited in BAuA, 2006; available at: http://www.baua.de/de/Themen-von-A-Z/Gefahrstoffe/TRGS/pdf/900/900-phenylisocyanat.pdf).

9. **Nehez, M., G.W. Fischer, I. Nehez, H. Scheufler, I. Desi:** Investigations on the acute toxic, cytogenetic, and embroyotoxic activity of phenyl isocyanate and diethoxyphosphoryl isocyanate. *Ecotoxicol. Environ. Saf. 17*: 258–63 (1989).

10. **Schreiber, G.:** Fraunhofer-Institut für Toxikologie und Aerosolforschung Schmallenberg, unveröffentlichter Bericht vom 09.07.1980 an die Bayer AG

11. **BAuA (Federal Institute for Occupational Safety and Health), 2006:** Begründung zu Phenylisocyanat in TRGS 900. Available at: http://www.baua.de/de/Themen-von-A-Z/Gefahrstoffe/TRGS/pdf/900/900-phenylisocyanat.pdf .

12. **Schreiber, G.:** Fraunhofer-Institut für Toxikologie und Aerosolforschung Schmallenberg, unveröffentlichter Bericht vom 09.07.1980 an die Bayer AG.

13. **Vernot, E.H., MacEwen, J.D., Haun, C.C., Kinkead, E,R,:** Acute toxicity and skin corrosion data for some organic and inor ganic compounds and aqueous solutions. *Toxicol Appl Pharmacol 42)*:417–23 (1977).

14. **ICI (Imperial Chemical Industries, Ltd):** Phenyl Isocyanate: Acute Inhalation Toxicity. Study No. HR0081. Report No. CTL/T/1098. Imperial Chemical Industries, Ltd., Central Toxicology Laboratory, Macclesfield, Cheshire, UK. October 1977.

15. **Pauluhn, J.:** Phenylisocyanat: Untersuchungen zur akuten Inhalationstoxizität an der Ratte. Report No. 20354. Bayer AG Institut für Toxikologie, Wuppertal, Germany. June 12, 1991 (unpublished).

16. **Sangha, G.K., Matijak, M., Alarie, Y.:** Comparison of some mono- and diisocyanates as sensory irritants. *Toxicol. Appl. Pharmacol. 57*:241–46 (1981)

17. **Pauluhn, J.:** Analyse experimenteller Methoden zur Bewertung der isocyanatinduzierten Lungenschädigung im Tiermodell. Institut für Experimentelle Pathologie der Medizinischen Hochschule Hannover, Fachbereich Toxikologie der Bayer AG, Wuppertal, Habilitationsschrift für das Fach Experimentelle Onkologie der Medizinischen Hochschule Hannover (1995).

18. **Pauluhn, J., W. Rüngeler, and U. Mohr:** Phenyl isocyanate-induced asthma in rats following a 2-week exposure period. *Fundam. Appl. Toxicol. 24*:217–28 (1995).

19. **Pauluhn, J.:** Different Methods used in Acute Subchronic Inhalation Studies with Potential Lung Irritants with Particular Attention to Lung Function Measurements. In U. Mohr (ed.), *Inhalation Toxicology – The Design and Interpretation of Inhalation Studies and Their Use in Risk Assessment.* Verlag: Springer, 1988. pp. 87101.

20. **Rosiello, A.P., J.M. Essigmann, and G.N. Wogan:** Rapid and Accurate Determination of the Median Lethal Dose (LD50) and its Error with Small Computer. *J. Tox. and Environ. Health 3*:797–809 (1977).

21. **Pauluhn, J.:** Phenylisocyanat; Untersuchungen zur orientierenden subakuten inhalationstoxizität an der Ratte (Exposition: 5 x 6 h/Tag). Bericht-Nr. 20132, Bayer AG Institut für Toxikologie. Bayer AG Institut für Toxikologie, Wuppertal, Germany. March 28, 1991 (unpublished).

22. **Pauluhn, J.:** Phenylisocyanat; Untersuchungen zur subakuten inhalationstoxizität an der Ratte (Exposition: 20 x 6 h/Tag). Bericht-Nr. 22415, Bayer AG Institut für Toxikologie. Bayer AG Institut für Toxikologie, Wuppertal, Germany. July 26, 1993 (unpublished).

23. **Li, W.L. and J. Pauluhn:** Mechanisms Involved in the Inhalation Toxicity of Phosgene (Chapter 19). In *Inhalation Toxicology*, 3rd edition. Salem, H. and S.A. Katz (eds.). New York: CRC Press, 2015. pp. 459–488.

24. **Herbold, B.:** Phenylisocyanat: Salmonella/Mikrosmen-Test zur Untersuchung auf Punktmutagene Wirkung. Report No. 9170. Bayer AG Institut für Toxikologie, Wuppertal, Germany. May 20, 1980 (unpublished).

25. **Andersen, M., M.-L. Binderup, P. Kiel, H. Larsen, and J. Maxild:** Mutagenic action of isocyanates used in the production of polyurethanes. *Scand. J. Work Environ. Health 6*:221–26 (1980).

26. **Melnikow, J., J.R. Keeffe, and R.L. Bernstein:** (1981). Cited in BAuA, 2006: Begründung zu Phenylisocyanate in TRGS 900. Available at: http://www.baua.de/de/Themen-von-A-Z/Gefahrstoffe/TRGS/pdf/900/900-phenylisocyanat.pdf?__blob=publicationFile.

27. **Yamaguchi, T.:** Mutagenicity of Isothiocyanates, Isocyanates and Thioureas on Salmonella typhimurium. *Agri. Biolog. Chem. 44*:12: 3017–18 (1980).

28. **Szybalski, W.:** Special microbiological systems. Screening Procedures for Experimental Cancer Chemotherapy. II. Observations on chemical mutagenesis in microorganisms. *Ann. New York Acad. Sci. 76*:475–89 (1958).

29. **Jarai, M.:** Action of mutagenic agents on auxotrophic strains of Streptomyces. *Acta Microbiol. Acad. Sci. Hung. 9*:273–84 (1962).

30. **Herbold, B.:** Phenylisocyanat: Micronucleus Test on the Mouse. Report No. 19566. Bayer AG, Fachbereich Toxicology, Wuppertal, Germany. September 9, 1990 (unpublished).

31. **Karol, M.H. and J.A. Kramarik:** Phenyl isocyanate is a potent chemical sensitizer. *Toxicol. Lett. 89*:139–46 (1996).

32. **Nakamura, A., et al.:** A new protocol and criteria for quantitative determination of sensitization potencies of chemicals by guinea pig maximization test. *Contact Derm. 31*:72–85(1994)

33. **Pauluhn, J.:** Phenylisocyanat: Untersuchungen zum Lungensensibilisierungspotenzial am Meerschweinchen nach intradermaler und einmaliger inhalativer Induktion. Report No. 23610 (1995). Bayer AG Institut für Toxikologie, Wuppertal, Germany (unpublished).

34. **Pauluhn, J.:** Phenylisocyanat – Orientierende Untersuchungen zur Lungensensibilisierung am Meerschweinchen nach intradermaler Induktion. Report No. 22159 (1993). Bayer AG Institut für Toxikologie, Wuppertal, Germany (unpublished).

35. **DFG (Deutsche Forschungsgemeinschaft):** The MAK Collection for Occupational Health and Safety: Phenyl isocyanate, published online January 31, 2012. Available online at: http://onlinelibrary.wiley.com/doi/10.1002/3527600418.mb10371e0017/pdf [accessed October 4, 2015].

36. **ECHA:** Exp WoE Skin sensitisation.003 and Exp WoE Skin Supporting Respiratory *sensitisation*.002, Available online at: http://echa.europa.eu/registration-dossier/-/registered-dossier/12563/7/5/2[accessed May 4, 2016].

37. **Tinnerberg, H., C.J. Sennbro, and B.A. Jönsson:** Aniline in hydrolyzed urine and plasma--possible biomarkers for phenylisocyanate exposure. *J. Occup. Environ. Hyg. 5*:629–32 (2008).

38. **Pauluhn, J.:** A mechanistic Approach to Assess the Inhalation Toxicity and Hazard of Methylisocyanate and Related Aliphatic Monoisocyanates. In *Assessment of Inhalation Hazards*. ILSI Monographs. Mohr, U. (ed.). Springer Verlag Heidelberg, 1989. pp. 119–128.

39. **Pauluhn, J. and U. Mohr:** Inhalation studies in laboratory animals – Current concepts and alternatives. Review. *Toxicol Pathol 28*:734–53 (2000).

40. **ten Berge, W.F. and A. Zwart:** More efficient use of animals in acute inhalation toxicity testing. *J. Hazard. Materials 21*:65–71 (1989)

41. **Zwart, A., J.H.E. Arts, W.F. ten Berge, and M. Appelman:** Alternative acute inhalation toxicity testing by determination of the concentration-time-mortality relationship: *Regulat. Toxicol. Pharmacol. 15*:278–90 (1992)

42. **Pauluhn, J.:** Time Scaling of Dose and Time to Response: The Toxic Load Exponent (Chapter 6). *Inhalation Toxicology,* 3rd edition. Salem, H. and S.A. Katz (eds.). New York: CRC Press, 2015. pp. 121–136.

43. **National Research Council (NRC):** Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals Subcommittee on Acute Exposure Guideline Levels. Washington, D.C.: Committee on Toxicology Board on Environmental Studies and Toxicology Commission on Life Sciences. National Research Council National Academy Press, 2001. Available at: http://www2.epa.gov/sites/production/files/2015-09/documents/sop_final_standing_operating_procedures_2001.pdf

44. **National Research Council (NRC):** Acute Exposure Guideline Levels for Selected Airborne Chemicals: Monoisocyanates Volume 15, pp. 200 (2013). Available at http://www.nap.edu/catalog/18449/acute-exposure-guideline-levels-for-selected-airborne-chemicals-volume-15. [Accessed October 4, 2015].

45. **National Research Council (NRC):** 2009: Acute Exposure Guideline Levels (AEGLs), Interim, Phenyl isocyanate. Document downloaded in 2015 at http://www.nap.edu website. This document was no longer available at this website on May 5, 2016.

46. **Whalan, J.E., J. Pauluhn, A.D. Kraft, and S. Makris:** 2015: The Impact of Rodent Reflex Bradypnea on Human Health Risk Assessments of Inhaled Irritants. Affiliation: U.S. EPA, National Center for Environmental Assessment, except JP: Bayer Pharma AG-Toxicology (retired), Wuppertal, Germany. 54th Annual Meeting of the American Society of Toxicology, San Diego, USA, March 22-26 (Poster#2612). The Toxicologist 2015, Late?Breaking Abstracts).

47. **Gordon, C.J., P.J. Spencer, J. Hotchkiss, D.B. Miller, P.M. Hinderliter, and J. Pauluhn:** Thermoregulation and its influence on toxicity assessment. *Toxicol. 244*:87–97 (2007).

48. **Swedish Work Environment Authority (SWEA):** Occupational exposure limit values and measures against air contaminants. AFS 2005:17 (2005).

49. **TRGS 900 (Technische Regeln für Gefahrstoffe:** Phenylisocyanat, BArBI Heft 1/2006. 2006. pp. 36. Available at: http://www.baua.de/cae/servlet/contentblob/666762/publicationFile/55588/TRGS-900.pdf

50. **Alarie, Y.:** Sensory irritation by airborne chemicals. *CRC Crit. Rev. Toxicol 2*:299–363 (1973).