Preliminary Risk assessment for Acrylamide and Peripheral Neuropathy

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ABSTRACT

Acrylamide (ACM) is a high-volume industrial chemical with diverse uses in manufacturing, construction and laboratory research. ACM is a well-established neurotoxic agent causing peripheral neuropathy with impairment in the arms and legs of exposed workers, most thoroughly studied in Swedish tunnel workers exposed to ACM grouting. A quantitative risk assessment was performed to assess ACM risk to workers. Using data from a published paper investigating peripheral neuropathies in Chinese chemical workers, estimates of exposure response for vibration perception threshold and nerve conduction velocities were calculated, based on hemoglobin adducts and air concentrations as exposure metrics. The benchmark dose procedure was applied in order to calculate excess risks of impairment, defined as adverse performance exceeding the 95th percentile in unexposed populations, at various concentrations of airborne ACM exposure. Under the assumptions in this risk assessment, after three years of inhalation exposure at $0.3 \, mg/m^3$, the excess attributable impairment manifest in vibration perception and nerve conduction velocity is estimated to occur in 1-2% of workers. For 10 years at $0.3 \, mg/m^3$ ACM inhalation (equivalent to 3 years at $1.0 \, mg/m^3$) the excess prevalence of impairment would be 2-14% of workers, assuming the effect continues to accrue linearly in time. Using published data, the risks of impairment from peripheral neuropathy attributable to exclusively airborne ACM exposure can be predicted for exposure periods less than 10 years. The risks associated with dermal and airborne ACM exposures can be estimated by characterizing working process environments using ACM Hb-adduct levels and possibly monitored with urinary biomarkers.

What is already known about this subject?

The neurophysiological effects of acrylamide exposures have been well established although the long-term effects and degrees of reversibility are uncertain.

What are the new findings?

A quantitative risk assessment is needed to guide prevention and for regulatory purposes, and was performed using published data from a chemical industry study.

How might this impact on policy or clinical practice in the foreseeable future?

The risk estimates from this study would inform regulatory standard-setting and would assist diagnostic and patient-care decisions in workers presenting with peripheral neuropathies and having potential acrylamide exposures.

1. Introduction

Acrylamide (ACM) is a major raw material in plastics production (acrylics), a grouting agent in construction and mining, a flocculation agent in water treatment and mining (Hills and Greife, 1986; Pennisi

et al., 2013), and in laboratories is used to make polyacrylamide chromatography gels. The most well studied human health effects of ACM are peripheral neuropathies (Calleman et al., 1994; Pennisi et al., 2013): nerve damage affecting arms, hands, legs and feet; symptoms include: numbness, tingling, cramps, sweating, and skin loss. Central nervous system effects include: headache, dizziness, dyspnea, nausea (Calleman et al., 1994; Hagmar et al., 2001; Pennisi et al., 2013). Experimental animal studies have revealed that ACM reduces axonal transport (Miller and Spencer, 1984; Gold et al., 1985) leading to a dying-back neuropathy (Schaumburg et al., 1974) and axonal swelling (Pennisi et al., 2013). Sensory axonal connections to the Pacinian corpuscles, which are involved in vibratory perception, undergo early degeneration with ACM exposure (Schaumburg et al., 1974; Spencer and Schaumburg, 1974).

The National Toxicology Program has determined that ACM is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals (https://ntp.niehs.nih.gov/ntp/roc/content/profiles/acrylamide.pdf). Some human evidence suggests excess lung and pancreatic cancer (Marsh et al., 1999) in a study with possible survivor bias: 70% of workers had less than 5 yrs employment, and the mean duration of ACM exposure was 1.69 yrs. In a further update of that cohort, the risk ratio for pancreatic cancer mortality, adjusted for smoking, in workers with 0.3 or more mg/m^3-yr ACM exposure was 2.05 (95% CI = 0.84-5.02) (Marsh et al., 2007). Based on mechanistic and animal findings, IARC in 1990 concluded that acrylamide is probably carcinogenic to humans (Group 2A) (IARC, 1994). Numerous investigations and risk assessments were performed following the discovery that acrylamide is generated in some food preparation processes involving high temperatures (Xu et al., 2014; Mucci and Wilson, 2008). Those assessments were focused on dietary intake of acrylamide and generally found no excess risk of neurological outcomes; the long-term carcinogenicity risk is less clear (Xu et al., 2014).

Studies of health effects from high ACM exposures have been conducted in Swedish workers constructing tunnels (Hagmar et al., 2001; Kjuus et al., 2004; Goffeng et al., 2008; OSHA, 2020) as well as in chemical manufacturing (Calleman et al., 1994; Bachmann et al., 1992; ACGIH, 2005). In chemical workers the ACM exposure air concentrations are generally below 0.3 mg/m^3 but can exceed 1 mg/m^3 in some workplaces. Dermal contact with aqueous solutions of ACM is another important route of exposure (Hagmar et al., 2001; Kjuus et al., 2004; Goffeng et al., 2008).

In this work, a quantitative risk assessment was performed. Data available from a study of Chinese chemical workers producing acrylamide (Calleman et al., 1994) was analyzed to estimate risks of impairment from peripheral neuropathies as a function of ACM airborne exposure concentrations or levels of ACM-hemoglobin adducts in the blood. The current U.S. OSHA Permissible Exposure Limit (PEL) for ACM is 0.30 mg/m^3 and the NIOSH Recommended Exposure Limit (REL) is 0.03 mg/m^3. Of these, the NIOSH REL stems from a risk assessment using animal bioassay data on carcinogenicity (NIOSH, 2020).

2. MATERIALS AND METHODS

2.1. Chinese Chemical Workers

From the study of Chinese chemical workers by Calleman et al., individual data for vibration perception threshold (VPT) were available from published tables as well as group data for motor and sensory nerve conduction velocities (NCV)(Calleman et al., 1994). Individuals with diabetes mellitus or nervous system disease had been excluded; four workers employed less than 6 months were excluded from the regression analyses reported (Calleman et al., 1994). The other significant exposure was the starting material for acrylamide synthesis, acrylonitrile, which at very high exposures (poisonings) has general CNS effects resulting from metabolic production of hydrogen cyanide. As discussed by Calleman et al. (Calleman et al., 1994) acrylonitrile was not a plausible

important contributor to peripheral neuropathy in the Chinese chemical workers. Also the risk factor, chronic hand-arm vibration stress, would not have been generally present in this process environment.

For the VPT outcome ACM exposure as air concentration was estimable from measured blood levels of hemoglobin (Hb) N-terminal valine-ACM adducts; for the NCV outcome, facility average ACM air concentrations were reported. A urinary metabolite of ACM, S-(2-carbamoylethyl) cysteine (CEC), was also reported for the VPT observations (Calleman et al., 1994). A literature search identified no other publications presenting individual-level or summary data permitting estimation of exposure response for neurophysiological outcomes other than symptoms, or, reporting such analyses. The literature on ACM health effects from ACM grouting agents in tunnel construction, while extensive, did not report associated ACM air concentrations or individual Hb-adduct levels, and exposures were primarily dermal (Hagmar et al., 2001; Kjuus et al., 2004; Goffeng et al., 2008).

Acrylamide-associated Hb-adduct levels are affected by dietary and smoking behaviors (Vesper et al., 2008). The neurophysiological end-points depend on age (Halonen, 1986; Deng et al., 1993; Deshpande et al., 2008; Lindsell and Griffin, 2003) and height (Halonen, 1986; Deshpande et al., 2008). The VPT end-point does not depend on gender when accounting for age and height (Halonen, 1986; Deshpande et al., 2008). Individual demographic information for the Chinese workers exposed to ACM was not available but it was a relatively young population, ages ranging from 18 to 42, and there were 34 men and 7 women; the average duration of exposure was 3 years (Calleman et al., 1994).

2.2. Reported Association of Acrylamide Hb-adduct levels with Air Concentrations

From a graphical presentation of a regression analysis reported by Jones et al. (Jones et al., 2006) the relation between ACM air levels and hemoglobin adducts was derived. Sixty workers were followed over 3 months, each worker providing 2-13 paired full-shift air and adduct samples. The Hb adduct has a time-constant of about 40 days (Calleman et al., 1994) and the Jones et al. adduct levels were stable over the study indicating a steady-state reflecting air exposures over the prior several months.

2.3. Outcomes Used for Assessment of Risk

The VPT outcomes in the Chinese workers, as foot and hand vibration thresholds, were measured using the Vibratron II tester (Physitemp Instruments Inc., Clifton, PA) (Calleman et al., 1994) and were reported in vibration amplitude units (VU) from which the VPT measure was calculated according to the method of Deng et al. (Deng et al., 1993): VPT = $0.5 \times VU^2$. A log-normal distribution of VPT in a normal population was reported by Deshpande et al. (Deshpande et al., 2008) and the mean and variance of NCV in normal populations was available from several sources (Deshpande et al., 2008; Sińczuk-Walczak et al., 2010; Trajaborg, 1964; King and Ashby, 1976). Regression models predicting outcomes (as VU) were fit using the biomarker values as linear and quadratic terms; cumulative biomarker predictors were biomarker levels multiplied by workers' exposure durations (years).

For nerve conduction, velocities were measured using the Dantec 2000C electroneuromyographic instrument recording with concentric needle electrodes (Calleman et al., 1994) and the difference in conduction velocity means between the ACM-exposed (n = 41) and an internal reference group (n = 80) was divided by the average ACM air concentration to yield an estimate of exposure response (over a 3 year period – average duration).

2.4. Risk Assessment

For risk assessment, the benchmark dose (BMD) procedure was applied for continuous exposure metrics (Crump, 1995; Bailer et al.,

1997; Park and Gilbert, 2018) which assumes that a normally distributed outcome measure is shifted as a result of exposure based on a regression estimate of exposure response. In this instance, impairment was defined and specified for VPT as an adverse observation above the 95%ile of normal and, for NCV, below the 5%ile of normal. The additional proportion of impairment was calculated as a function of the exposure metric used in regression models (VPT) or for the exposure response calculated for NCV (see Appendix for BMD procedure). The calculations depended on variance estimates reported in normal populations for VPT (Deng et al., 1993; Deshpande et al., 2008) and for NCV (Deshpande et al., 2008; Sińczuk-Walczak et al., 2010; Trajaborg, 1964; King and Ashby, 1976). Because ACM exposures in some kinds of work are primarily via the dermal route, a risk assessment based on Hb-adduct in blood was also performed. This calculation applied the regression result using the VPT data reported by Calleman et al. (Calleman et al., 1994).

3. RESULTS

3.1. Vibration Perception Threshold

From Jones et al. (published Fig. 2) (Jones et al., 2006) the following relationship between blood Hb adduct and ACM air concentration was derived from a graph: $Hb_{add} = 10 [ACM]^{0.87}$ or $[ACM] = (Hb_{add}/10)^{1.15}$ (where Hb_{add} is in pmol/g globulin and ACM is in µg/m^3). Moorman et al. also reported the ACM – Hb-adduct relationship (Moorman et al., 2012) based on fewer data-points (a single several-hour air sample from 27 workers vs. 2-13 full-shift air samples from 60 workers over 3 months). The Moorman et al. work estimated an adduct level of 1.0 nmol/g at an air level of 1.0 mg/m^3 (Moorman et al., 2012) whereas the Hb-adduct estimate from Jones et al. was 4.0 nmol/g. The estimate from the Jones data was used because it was thought to be more representative of long term, steady state, exposure conditions. Also, the Hb adduct determination procedure of Jones et al. (Jones et al., 2006) may have been more compatible with that used in Calleman et al. (Calleman et al., 1994) than would be that of the more recent work by Moorman et al. (Moorman et al., 2012).

Simple linear regression analyses of vibration unit (VU) for foot and hand vibration thresholds in the Chinese worker population show statistically significant associations with both duration of ACM exposure and the biomarker metrics; the association for foot VU was the strongest (Table 1, Supplemental Fig.1). The best predictor for foot and hand VU was cumulative Hb_{add} with little or no improvement upon including a quadratic term. The urinary biomarker (CEC) representing only recent ACM exposure was a poor predictor of VU; the quadratic term considerably improved model fit, and the cumulative term was less predictive. From Deshpande et al. (published Fig.1) (Deshpande et al., 2008) the variance in VPT for normals was derived from graph as a standard deviation: $StdDev(log_{10}(VPT)) = 0.55$ (see Appendix). The dependence of VPT on height is small (<2% variation across quintiles in a normal population (Deng et al., 1993) and on age would have varied by 10% over the age range of the Chinese study (Deng et al., 1993).

Applying the regression results relating a) ACM air concentrations to Hb-adduct levels from Jones et al. (Jones et al., 2006) and b) adduct levels to vibration perception thresholds (Table 1), in the BMD procedure, for an exposure period of 3 years (average duration in the Chinese workers) shows that ACM exposures at the current OSHA PEL (0.30 mg/m^3) confer an estimated excess risk of impairment of 7-21 per 1000 workers (0.7 -2.1%) (Table 2), where impairment is defined as VPT above the 95%ile of normal. Based on the foot VPT analysis with cumulative ACM exposure over 3 years, one per thousand excess impairment would result from an ACM exposure of 0.01 mg/m^3 (0.03/2.8) (Table 2).

3.2. Nerve Conduction Velocities

For nerve conduction velocities, the Chinese ACM workers were compared to a historical control group of unexposed workers (Calleman et al., 1994) (Table 3). All three motor nerve tests showed reduced velocities with ACM exposure as did two of three sensory nerve tests: for the ulnar and sural nerves. Normal values were extracted from several published studies (NIOSH, 2020; Deng et al., 1993; Deshpande et al., 2008; Lindsell and Griffin, 2003) from which summary values of means and standard deviations were specified (Table 4) for use in the BMD procedure where the estimates of exposure response were applied. (The mean value from normal populations has no effect on the excess impairment calculation in the BMD procedure which depends only the standard deviations.)

Benchmark dose estimates for 3 years of ACM exposure indicate that at the current OSHA PEL the excess risk of impaired nerve conduction

Table 1

Regression models of vibration perception threshold (VPT, in VU units) with Hb-adduct and CEC biomarkers in Chinese ACM workers

model	Biomarker	Rsq	Intcp	beta	p	beta2	p2
	Foot Vibration Perception Threshold						
1	Duration (yrs)	.260	2.92	0.811	.0001		
2	CEC	.009	4.99	0.0071	.50		
3		.172	3.32	0.083	.0007	-.00030	.0036
4	cumCEC	.160	4.17	0.0068	.0037		
5	Hb_{add}	.195	3.42	0.246	.0012		
6		.204	2.98	0.384	.067	-.0049	.48
7	$cumHb_{add}$	.505	3.03	0.076	<.0001		
		.506	2.90	0.086	.0026	-.00006	.71
	Hand Vibration Perception Threshold						
1	Duration (yrs)	.152	1.82	0.144	.005		
2	CEC	.034	2.10	0.0032	.195		
3		.259	1.64	0.024	.0002	-.000082	.0004
4	cumCEC	.171	1.97	0.0016	.0025		
5	Hb_{add}	.251	1.74	0.065	.0002		
6		.256	1.67	0.088	.061	-.00082	.59
7	$cumHb_{add}$	.387	1.78	0.016	<.0001		
		.402	1.69	0.022	.0022	-.00004	.28

VU – vibration amplitude units; CEC – urinary S-(2-carbamoylethyl) cysteine, µmol/24 hr urine;
$cumCEC$ – cumulative CEC; Hb_{add} – hemoglobin N-terminal valine - ACM adduct, nmol/gm globin;
$cumHb_{add}$ – cumulative Hb_{add}; Rsq - regression R squared; Intcpt - regression intercept
Model: $VU = a + beta \times BioMkr + beta2 \times BioMkr^2$
[p] – two-tailed p-value for beta p2 – two-tailed p-value for beta2

Table 2

Excess risk of vibration perception impairment and nerve conduction impairment with 3 years of ACM inhalation exposure by benchmark dose calculation (per 1000)

End-point	ACM, constant concentration in air over 3 years				
mg/m³	0.01	0.03 (REL)	0.10 (EU)	0.30 (PEL)	1.0
µg/m³	10	30	100	300	1000
	Vibratory Perceived Threshold (VPT) impairment prevalence /1000				
VPT, foot (cum adduct)[1]	1.2	2.8	7.6	20.6	65.7
VPT, hand (cur adduct) *[2]	0.5	1.3	3.6	9.7	29.7
VPT, hand (cum adduct) *[3]	0.4	1.0	2.7	7.0	20.9
	Nerve conduction velocity impairment prevalence /1000[4]				
MCV, median nerve	0.2	0.6	2.1	6.5	24.4
MCV, ulnar nerve	0.2	0.6	2.2	6.8	25.6
MCV, peroneal nerve	0.4	1.1	3.7	11.4	47.2
SCV, median nerve	0.3	1.1	3.5	10.8	44.6
SCV, sural nerve	0.8	2.4	8.3	26.1	135.3

* Using normal SD based on foot data

REL – U.S. NIOSH Recommended Exposure Limit; EU – European Commission occupational exposure limit;

PEL – U.S. OSHA Permissible Exposure Limit; MCV – motor conduction velocity; SCV – sensory conduction velocity

1 using Table 1, foot VPT, model 7: beta = 0.076

2 using Table 1, hand VPT, model 5: beta = 0.065

3 using Table 1, hand VPT, model 7: beta = 0.016

4 using exposure response, XR (for 3 yr average duration), from Table 3 (population SD not available for sensory ulnar nerve)

would be 7-26 per 1000 (0.7 -2.6%), in the same range as estimates based on vibration perception (Table 2).

3.3. Dermal Exposure in Chinese Chemical and Swedish Tunnel Workers

Applying the relation between Hb-adducts and ACM air concentrations from Jones et al (Jones et al., 2006) to the Hb-adduct data from the Chinese chemical workers implies that the equivalent air concentrations had a median, mean and 90%ile of 1.6, 2.3 and 6.6 mg/m³, respectively (Supplemental Fig. 2). These levels are consistent with mean ACM air concentrations reported from 1991 in the Synthesis and Polymerization areas of the plant which ranged 0.58 to 5.95 mg/m³, and depended on season (Summer vs. Autumn) (Calleman et al., 1994). For these chemical workers whose Hb-adduct levels ranged 0.3 to 35 nmol/gm, the BMD procedure predicts excess impairment of 0.4 % to >40 % over 3 years of acrylamide exposure (Table 5).

The tunnel workers can be assumed not to be exposed to ACM dusts because the grouting product used was always in water solution but could have some ACM - containing mist and vapor exposure. In the Swedish tunnel workers (Hagmar et al., 2001), the average air concentrations of ACM was 0.15 mg/m³ but Hb-adduct levels in five workers

Table 4

Normal values for nerve conduction velocities with summary values from published studies for use in BMD procedure.

Mean m/sec	SD	SE	n	Source/table
motor conduction velocity, median nerve				
58.1	7.60	1.96	16	Table 6[22]
67.9	7.7	1.6	24	Table III[23]
56.1	5.3	0.9	36	Table III[23]
60.5	4.8	1.0	24	Table III[23]
60	6.48[1]			Summary
motor conduction velocity, ulnar nerve				
63.4	5.3	1.1	22	Table III[23]
56.4	4.8	0.9	30	Table III[23]
59.4	4.1	0.9	22	Table III[23]
67.0	6.8	1.7	17	Table 1[24]
56.0	6.3	1.6	17	Table 1[24]
60	5.55[1]			Summary
motor conduction velocity, peroneal nerve				
54.3	4.80	1.239	16	Table 6[22]
53.5	4.70	1.214	16	Table 6[22]
47.4	7.4	0.32	523	Table 1[19]
53	5.77[1]			Summary
sensory conduction velocity, median (m) or sural (s) nerve				
59.0 (m)	7.00	1.807	16	Table 7[22]
60	7.00			Summary
60.0 (s)	5.60	1.446	16	Table 7[22]
46.4 (s)	7.6	0.33	523	Table 1[19]
55	6.76[1]			Summary

1. Root mean square of reported SDs

Nerve conduction velocity: m/sec

(2.2-4.3 nmole/g globin) corresponded to high air concentrations 0.5 - 1.1 mg/m³ based on Jones et al. (Jones et al., 2006), implying that much of their exposure burden was via the dermal route. For the observed Hb-adduct levels in tunnel workers the BMD predicted excess impairment prevalence after 2 months would be 0.1-0.4% of workers (Table 5); after 3 years the predicted excess prevalence of impairment would be 3-8%. These tunnel workers were also exposed to lower (than ACM) levels of N-methylolacrylamide, believed to be less neurotoxic (Hagmar et al., 2001).

The Hb-adduct determination procedures described by Sams et al. (Sams et al., 2015) appear to be more sensitive than earlier methods such as those used by Jones et al. (Jones et al., 2006) or Bergmark et al. (Bergmark et al., 1993) that were used in this risk assessment. The concentrations of Hb-adduct predicted from air concentrations corresponding to the than those estimated here from Calleman et al. (Calleman et al., 1994).

4. DISCUSSION

4.1. Findings

After three years of constant occupational ACM exposure at an air concentration of 0.3 mg/m³ attributable impairment, manifest in

Table 3

Nerve conduction velocities in Chinese ACM workers

End-point	NCV ACM workers	SD	NCV Reference workers	SD	ACM conc.	XR	var(XR)
MCV, median nerve	56.8	7.2	59.6	5.0	2.17	1.29	0.42
MCV, ulnar nerve	60.0	9.2	62.5	5.4	2.17	1.15	0.66
MCV, peroneal nerve	43.8	8.5	48.1	3.5	2.17	1.98	0.53
SCV, median nerve	61.6	5.8	60.3	4.1	2.17	−0.60	0.28
SCV, ulnar nerve	61.9	6.4	66.9	4.3	2.17	2.30	0.33
SCV, sural nerve	46.6	6.6	56.8	4.0	2.17	4.70	0.34

NCV – nerve conduction velocity, in m/sec; NCV data from: Table 4 in Calleman et al. (Calleman et al., 1994); ACM conc. – facility average exposure conc., mg/m³; XR – exposure response: XR= (NCV(Ref)-NCV(ACM)/ACM; XR in (m/sec)/(mg/m³) = m⁴/mg.sec; MCV – motor conduction velocity; SCV – sensory conduction velocity

Table 5
Benchmark dose calculations of excess risk of vibration perception impairment (in the foot) based on the biomarker Hb-adduct levels.

ACM air conc.[1] mg/m^3	Excess Hb-adduct[2] nmol/gm	Excess Hb-adduct[3] nonsmokers nmol/gm	Excess Hb-adduct[4] smokers nmol/gm	Excess risk of Foot VPT impairment after 3 years /1000	Range of observed Hb-adduct in Chinese chemical workers[2] at 3 yr	Excess risk of Foot VPT impairment at 2 months /1000	Range of observed Hb-adduct in Swedish tunnel workers[1] at 2 mo
0.0001	0.001	0.032	0.053	0.26		0	
0.0002	0.002	0.052	0.086	0.28		0	
0.0005	0.005	0.100	0.167	0.31		0	
0.0010	0.01	0.165	0.274	0.38		0	
0.0022	0.02	0.272	0.451	0.51		0	
0.0064	0.05	0.524	0.871	0.90		0	
0.014	0.1	0.862	1.432	1.53		0	
0.031	0.2	1.417	2.355	2.81		0.04	
0.090	0.5	2.734	4.545	6.82	X	0.26	
0.20	1	4.496	7.473	13.6	X	0.60	
0.44	2	7.393	12.289	28.1	X	1.3	X
1.27	5	14.267	23.719	79.8	X	3.5	X
2.82	10	23.459	39.004	177	X	7.1	
6.25	20	38.574	64.140	374	X	14.5	
9.97	30	51.598	85.801	-	X	-	

1. Calculated from Hb-adduct levels using Jones et al., 2006, Fig 2: $[ACM(air)] = (Hb_{add}/10)^{1.15}$
2. Excess Hb-adduct above baseline in general population, uncorrected for smoking or other demographic determinants, Calleman et al., 1994, Table 6
3. Calculated from Sams et al., 2015 (derived from Table 5): Hb-adduct (nonsmokers) $= 12.29 \times air^{0.624}$
4. Calculated from Sams et al., 2015 (derived from Table 5): Hb-adduct (smokers) $= 20.43 \times air^{0.624}$

ACM – acrylamide VPT – Vibratory Perceived Threshold

vibration perception and nerve conduction velocity, is estimated to occur 1-2% of workers. Evidence of some reversibility or recoverability has been reported (Hagmar et al., 2001; Kjuus et al., 2004; Goffeng et al., 2008). In tunnel workers, Hagmar et al. observed reduced symptoms (sensory perception thresholds and nerve conduction velocity or amplitudes) in 23 initially impaired workers after 12 months post exposure with only 3 workers still exhibiting neurophysiological symptoms (Hagmar et al., 2001). On the other hand, among tunnel workers whose Hb_{add} was greater than 0.3 nmol/gm, six months after last exposure their symptoms were unchanged (38%) or worsened (4%) (Hagmar et al., 2001). Goffend et al. observed persistent deficits in neurological outcomes (sural nerve conduction and visual evoked potentials) 16 months after exposure and, in a different population, some improvement two or more years after exposure, but the actual past exposures were not known. The effects were consistent with both axonal and myelin lesions (Goffeng et al., 2008).

After 10 years at 0.3 mg/m^3 (or three years at 1.0 mg/m^3) ACM the excess prevalence of impairment would be 2-14%, assuming the effect is irreversible and continues to accrue linearly in time. Ten years duration was actually within the observed range of the Chinese chemical workers: although the mean duration of ACM exposure (among those exposed) was only 3.7 years, 10% of workers had durations greater than 8 years (maximum: 11.5 yr) (Calleman et al., 1994). There was further support for the assumption of persistent impairment in the foot VPT regression analysis where *cumulative* exposure (based on Hb-adduct) was a better predictor than the *current* exposure metric. However, extrapolation to working lifetime exposure (45 years) was beyond the range of the observed data; there is no published record of the effects of prolonged ACM exposures over many years; impairment conceivably could progress at a faster (or slower) rate than predicted by cumulative exposure. An excess risk of one per thousand over 10 years, based on the most sensitive end-point (foot VPT) was associated with air concentration of about 0.003 mg/m^3 (Table 2; 0.03/2.8 × 3/10) and with an Hb-adduct level of about 0.02 nmol/g (Table 5; 0.05/0.9 × 3/10).

4.2. Limitations

VPT and NCV may not be the best outcomes for assessing neurological adverse effects from ACM. Nerve conduction amplitude would be preferable but this data was not available. Although defining impairment on a distributional basis, e.g., the 5th percentile of normal, would tend to produce similar risk estimates across adverse outcomes, it remains possible that using primarily the VPT (and secondarily NCV) may have underestimated ACM risk.

The contribution of diet and smoking to Hb-adduct levels in the Chinese workers studied would have been small. Smoking increases Hb-adduct levels by about 0.09 nmol/g Hb adduct (Vesper et al., 2008) or 0.02 nmol/g Hb adduct (Jones et al., 2006) and Hb-adduct levels in normal, non-smoking populations (i.e., from diet) range less than 0.10 nmol/g Hb (Hartmann et al., 2008); adduct levels in the Chinese study were 0.3 – 32 nmol/g Hb. Possible differences in VPT response by Chinese vs. Caucasian ethnicity are not known but for nerve conduction velocities there were no apparent differences comparing mean values from the Chinese reference group in this study (Table 3) with the non-Chinese normal values (Table 4).

The relation between air levels and Hb-adducts was taken from Jones et al. (Jones et al., 2006) and applied in the higher range of ACM exposures of the Chinese workers. If the observed attenuation in that relationship, $(Hb_{add} = 10 [ACM]^{0.87})$ embodied in the term, $ACM^{0.87}$, increases with increasing ACM air concentrations, then the predicted Hb-adduct level and associated impairment would be overestimated for a specified ACM exposure and the calculated BMD risks overstated.

Whether the Hb-adduct determination procedures have been compatible across studies has been questioned (Sams et al., 2015) in relation to the chemical standards used. For the Jones et al. derivation (Jones et al., 2006) of the air to Hb-adduct association as used in this risk assessment, there was limited data for comparison from Bergmark et al. (Bergmark et al., 1993), the investigators reporting the Hb-adduct determinations in the Chinese chemical workers analyzed here. In the polymerization department of the chemical workers with a reported mean air concentration of 1.52 mg/m^3 ACM, the Hb–adduct level measured was 7.3 nmol/g Hb (Bergmark et al., 1993) while the prediction based on Jones et al. was an adduct level of 5.6 nmol/g (Jones et al., 2006), lower by 30 percent. If the Hb-adduct determinations in Calleman et al. were systematically higher than those of Jones et al., then the air levels estimated from Hb-adduct levels the Chinese worker study would have been overestimated and the excess risks for inhalation exposures underestimated in this risk assessment. Among the synthesis chemical workers, the adduct level was four-fold higher than predicted from air levels (Bergmark et al., 1993), suggesting a large dermal

Table 6

Proposed inhalation and Hb-adduct occupational exposure limits (OEL) for acrylamide

Authority	Source	OEL mg/m^3	BEI/ BGV nmol/g Hb
U.S. EPA	*Toxicological review of acrylamide*; EPA/ 635/R-07/009 F, March 2010	0.025	-
European Commission	*Recommendation from the Scientific Committee on Occupational Exposure Limits for Acrylamide*, SCOEL/SUM/ 139, September 2011/Annex December 2012	0.10	-
Nonsmokers		-	0.08
smokers		-	0.29
California OEHHA	*Proposition 65 Proposed Maximum Allowable Dose Level (MADL) for Reproductive Toxicity for Acrylamide,* February 2010	0.025	-
U.S. OSHA PEL		0.30	-
U.S. NIOSH REL		0.03	-
This quantitative risk assessment	For 1/1000 excess risk @ 10 yr exposure	0.003[1]	0.02[2] 0.17[3]

OEL – Occupational Exposure Limit BEI – Biological Exposire Index BGV – Biological Guidance value

OEHHA – Office of Environmental Health Hazard Assessment PEL – Permissible Exposure Limit

REL – Recommended Exposure Limit

1. From Table 2, VPT, foot: 0.03 mg/m^3 for 3 yrs -> 2.8/1000 risk; for 10 yrs -> $10/3 \times 2.8 = 9.3/1000$; thus, 1/1000 risk at 0.03/9.3 = 0.0032 mg/m^3

2. From Table 5, Hb-adduct (Calleman et al., 1994 and Jones et al., 2006): 0.05 nmol/gm for 3 yrs -> 0.9/1000 risk; for 10 yrs -> $10/3 \times 0.9 = 3.0/1000$; thus, 1/1000 risk at 0.05/3.0 = 0.0167 nmol/gm

3. From Table 5, Hb-adduct (Calleman et al., 1994 and Sams et al., 2015): 0.524 nmol/gm for 3 yrs -> 0.9/1000 risk; for 10 yrs -> $10/3 \times 0.9 = 3.0/1000$; thus, 1/1000 risk at 0.524/3.0 = 0.173 nmol/gm.

contribution to exposure in that group. This interpretation is supported by an environmental assessment of Bull et al. (Bull et al., 2005) comparing polymerization and synthesis workers in a ACM and poly-acrylamide manufacturing plant in Europe.

Dermal ACM exposures are important in construction and some manufacturing processes (especially as aqueous solutions) but are difficult to quantify. Bull et al. developed measures of ACM dermal contact at an ACM and polyacrylamide manufacturing facility, using glove samples and surface swabs reflecting specific process conditions (Bull et al., 2005). Regression analyses demonstrated that a measure of surface contamination was a statistically significant predictor of urinary ACM metabolites but that ACM air concentrations and smoking represented "the major contribution to systemic exposure" (Bull et al., 2005). In contrast, tunnel worker exposures appeared to arise primarily from dermal exposure (Hagmar et al., 2001). For surveillance purposes in environments with high dermal exposure potential, metabolites or Hb-adducts (Table 5) may provide a feasible and valid means of process characterization and exposure assessment by way of biomarkers, possibly using a less intrusive, urinary biomarker for routine surveillance.

4.3. ACM Occupational Exposure Limits (OEL)

Regulations governing acrylamide, based on animal or human studies, include: a) from U.S. EPA, OEL = 0.025 mg/m^3 (*Toxicological review of acrylamide*; EPA/635/R-07/009 F, March 2010); b) from the European Commission, OEL = 0.1 mg/m^3 and Biological Guidance Values (BGV, human) of 0.080 and 0.285 nmol Hb-adduct/gm globulin for in nonsmokers and smokers, respectively (*Recommendation from the Scientific Committee on Occupational Exposure Limits for Acrylamide*, SCOEL/SUM/139, September 2011/Annex December 2012); and c) California Office of Environmental Health Hazard Assessment (OEHHA), OEL = 0.025 mg/m^3 (*Proposition 65 Proposed Maximum Allowable Dose Level (MADL) for Reproductive Toxicity for Acrylamide,* February 2010) (Table 6). The U.S. OSHA Permissible Exposure Limit (PEL) for ACM air concentrations is 0.3 mg/m^3 and the U.S. NIOSH Recommended Exposure Limit (REL) is 0.03 mg/m^3. None of these limits was derived from quantitative risk assessments in humans, and none (as in the present analysis) accounted for lifetime employment. Based on the present VPT analysis with cumulative exposure over just 3 years, one per thousand excess impairment would result from an ACM concentration of 0.011 mg/m^3 (from Table 2, VPT, foot: 0.03/2.8 = 0.0107) or one per hundred excess impairment from 0.11 mg/m^3 (Table 6). Over 10 years, one per thousand excess impairment would result from an ACM concentration of 0.003 mg/m^3 ($0.0107 \times 3/10$). The long term effects of ACM exposure are unknown and a consensus on the maximum acceptable level of impairment for conditions such as peripheral neuropathy resulting from short term exposures has not been established.

4.4. Conclusion

Using published data, the risk of impairment from peripheral neuropathy attributable to exclusively airborne ACM exposure was predicted for exposure periods less than 10 years. The risks associated with dermal and airborne ACM exposures can be estimated by characterizing working process environments using ACM Hb-adduct levels and possibly monitored with urinary biomarkers. The 1/1000 risk of impairment from ACM exposure for 10 years results from an estimated airborne exposure concentration of 0.003 mg/m^3 which is a factor of 10-100 below current OELs.

CRediT authorship contribution statement

The author performed all the preparation, analyses and writing for this work.

Disclaimer

Declaration of competing interest

The author declares that there are no competing interests.

Appendix A. Benchmark dose calculation in SAS software: foot VPT with cumulative ACM air exposure over 3 yrs (for Table 2)

```
data Aara.AaTradBNB3_1 ; * Footvibr(VU) for cumAAval metric ; * on cumX ;
 file 'C:\AaRA\AaTradBNB3_1.dat';
 xr001=.; xr002=.; xr005=.; xr01=.; xr02=.; xr05=.; xr10=.; xr20=.; xr50=.; xr1=.; xr2=.; xr5=.; xrt10=. ;
 sigma=0.55 ; * derived from Deshpande 2008[19], Fig 1 ;
 x=0.0001 ; * in mg/m3 ACM ;
 impT=0.75+1.64*sigma ;                    [ impairment threshold; 0.75 is mean for log10(VPT) in Deshpande 2008[19], Fig 1 ]
 bkgd=0.03 ;                               [ 0.03 is baseline AAHb at 1 ug/m3, in nmol/g, from Jones 2006[21] Fig 2 ]
 do while (x < 11.0 and xrt10= .) ;
   x=x+0.05*x ;
   AAHb=0.03+0.01*(1000*x)**0.877 ;        [ derived from Jones 2006[21], Fig.2: from pmol -> nmols (0.01) and  mg -> ug  (1000) ]
   cumAAHb=AAHb*3 ; * for avg emp. dur. = 3 yr ;
   VU=3.03+0.076*cumAAHb ;                 [ from Calleman 1994[6], nmols/g; Tbl6 -> regn @ Aa0215.1.19 – Table 1 above ]
   VPT=0.5*VU**2 ;                         [ Deng 1993[18] ]
   L10VPT=log10(VPT) ;
   mu=0.0875 + L10VPT ;                    [ 0.0875: BL to yield p=0.05 risk; derived from baseline BMD (for X=0)
                                             0.0875= 0.75 -  L10VPT(x=0)  = 0.75 − 0.6625  ]


* for case of impT= 1.652 and x=0 (mu=.75) cumR= 0.0505 ;


   cumR=1-CDF('NORMAL',impT,mu,sigma) ;                  [ using SAS cum distribution function  ]
   xcumR=cumR-0.05050 ;
     if xr001=. and x >= .001 then xr001=xcumR;          [ calculates excess risk as function of exposure ]
     if xr002=. and x >= .002 then xr002=xcumR;
     if xr005=. and x >= .005then xr005=xcumR;
     if xr01=. and x >= .01 then xr01=xcumR;
     if xr02=. and x >= .02 then xr02=xcumR;
     if xr05=. and x >= .05 then xr05=xcumR;
     if xr10=. and x >= .1 then xr10=xcumR;
     if xr20=. and x >= .2 then xr20=xcumR;
     if xr50=. and x >= .5 then xr50=xcumR;
     if xr1=. and x >= 1 then xr1=xcumR;
     if xr2=. and x >= 2 then xr2=xcumR;
     if xr5=. and x >= 5 then xr5=xcumR;
     if xrt10=. and x >= 10 then xrt10=xcumR;
   put (x VPT xr001 xr002 xr005 xr01 xr02 xr05 xr10 xr20 xr50 xr1 xr2 xr5 xrt10) (F8.4) ;
   output ;
 end ;
run ;
```

Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neuro.2021.04.004.

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