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Self-reported symptoms and neuropsychological function among tunnel workers previously exposed to acrylamide and N-methylolacrylamide

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Objective The aim of this study was to examine possible exposure-related symptoms and neuropsychological changes among tunnel workers previously exposed to grout containing acrylamide and N-methylolacrylamide.

Methods In a cross sectional study, 44 male tunnel workers previously exposed to acrylamide and N-methylolacrylamide during grouting operations were examined with neuropsychological tests, 2–10 years after last exposure. The control group consisted of 49 male tunnel workers with no history of acrylamide exposure. Questionnaires were used to assess retrospectively recalled symptoms during work and current symptoms at the time of the examination.

Results The prevalence of paresthesia in hands and legs and leg cramps during work periods were higher in the exposed than control group. Self-reported prevalence of skin irritation, peeling of skin on the hands, white-finger attacks, headache, and breathlessness was also higher among the exposed workers. The Q-16 questionnaire on current symptoms indicated higher symptom prevalence among the exposed of impaired memory and concentration, emotional change, sleep disturbances, tiredness, headache, and sensory or motor changes. In contrast, no association was found between neuropsychological test results and acrylamide exposure, adjusting for relevant confounders. However, selected motor symptoms were associated with the corresponding results on tests for motor function.

Conclusions Despite higher prevalences of self-reported current symptoms among the acrylamide-exposed compared to the control group, we did not find an association between occupational acrylamide exposure and health outcomes as measured by the chosen neuropsychological tests. Observed associations between chemical exposure and self-reported symptoms should be interpreted with great caution.

Key terms exposure; chemical exposure; cross sectional study; nervous system; occupational health; neuropsychological testing; persisting effect; questionnaire; grouting agent.

Tunnel construction includes excavation, with drilling, placement of explosives in the holes, and blasting, followed by the transport of broken rock out of the tunnel. Rock support is performed throughout the process and, after the excavation has been completed, followed by various finishing work. Major types of rock support materials are rock bolts, wet concrete, and cement- or chemical-based grout (1). Acrylamide-containing chemical grouts have been used during tunnel construction to fill cracks and crevices in rocks to prevent water-leakage into tunnels. Occupational exposure to acrylamide may, however, present a hazard for construction workers (2). The first known case of acrylamide-related peripheral nervous system health effects among tunnel construction

workers was in France in 1970 (3). Several reports have later related similar nervous system symptoms among tunnel workers to the use of such grouts (4, 5).

Grouts containing N-methylolacrylamide (NMA) were originally developed as a less toxic alternative to acrylamide, although the molecular structure of the two substances does not indicate different modes of toxic action. In addition, in tunnel construction, NMA-based grouts have led to a leakage of both acrylamide and NMA monomers, as NMA may be transformed to acrylamide at high pH of drainage water and due to a low degree of polymerisation if the product is diluted in water (6).

Acrylamide is classified as a probable human carcinogen (2, 7), and may have reprotoxic and mutagenic

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properties (8). Acute neurotoxic effects were seen among Swedish workers in a tunnel construction project where NMA-based grouts were used (9). We have previously reported possible genotoxic (10) and neurotoxic (11) effects among Norwegian tunnel workers using NMA-based grouts. Among the Norwegian tunnel workers, we found indications of reversibility of several symptoms, such as skin-irritation, paresthesia, and pain in the hands when the workers were examined 16 months post-exposure (11). Also slight neurophysiological effects in the peripheral nervous system (PNS) apparent at examination 4 months post-exposure were mostly normalized at examination 16 months post-exposure, effects thus regarded as transient and reversible. Only sural sensory nerve conduction velocity (NCV) impairment progressing from examinations 4–16 months was observed, but it could not be concluded whether this was an evolving persistent or delayed transient impairment.

In Norway, NMA grouts were used by workers in several large tunnel projects during the 1990s. Thus, in another group of acrylamide-exposed tunnel workers, examined 2–10 years post-exposure, we also observed a reduced sural NCV, indicating a possible persistent effect on the peripheral nervous system (12). In addition, we recently reported reduced visual system function related to color vision and light sensitivity among these tunnel workers, indicating persisting axonal visual system effects (12, 13).

In summary, there is neurophysiological empirical evidence both supporting an assumption that PNS effects are largely reversible (11) and that central nervous system (CNS) effects may persist (12, 13). The observed effects, however, seemed to be subclinical or of limited clinical relevance. Still, the relationship between self-reported symptoms and objective test results remains unclear.

Neuropsychological testing is a sensitive method for detecting persistent cognitive and psychomotor effects due to toxic exposure, but neuropsychological function among workers previously exposed to acrylamide has, to our knowledge, not been examined. Our aim is to describe the neuropsychological test profile and self reported symptoms among tunnel construction workers previously exposed to grout containing acrylamide and NMA (12). The study's main focus is motor symptoms and tests related to motor function, although the tests and questionnaires cover a variety of functional domains.

Methods

Subjects

Fifty male tunnel workers, who had been working in tunnel projects where NMA grout had been used more than two years prior to the examination, were available

for the study. They were recruited from four Norwegian companies listed in a registry of tunnel construction companies using acrylamide-containing grouts, established in 1997 by the Norwegian Association for Building and Construction Industry for surveillance purposes. Information from the construction companies and occupational health department files was used to identify possible study participants, and the workers were invited to participate based on the number of projects and amount of NMA-grouts used in each project (12).

Subjects with known alcohol or drug abuse were not eligible for the study. Two subjects (one with known diabetes mellitus and another with a probable cerebrovascular incident), were excluded from the exposed group. As the study addresses persistent nervous system effects, four subjects with a history of both previous and recent exposure to acrylamide/NMA were excluded, due to possible incomplete peripheral nerve-recovery following the more recent exposure (11). Accordingly, 44 eligible subjects were included in the index group of workers with previous NMA exposure.

Of the 53 male tunnel workers not previously exposed to NMA grouts, randomly recruited from one of the four construction companies and invited to participate as control group, 51 accepted to participate. One was excluded due to neurological disease (epilepsy) while another dropped out from parts of the study later on, leaving a final control group of 49 subjects.

The mean age of the 44 previously exposed workers was 47.9 years, compared to 44.6 years among the 49 controls (table 1). The duration of formal education was 9.6 [standard deviation (SD) 2.2] years for the previously exposed workers, and 10.2 (SD 2.0) years for the controls. The exposed group had been engaged in tunnel construction or other construction work for 24.6 (SD 12.5) years and the controls for 19.3 (SD 10.7) years. Due to causes unrelated to the outcome of this study, 11 of the exposed workers were out of work at the time of examination. The distribution of relevant occupational exposures and lifestyle factors (ie, smoking, alcohol consumption) are presented in table 1.

The project was undertaken in close cooperation with the companies' occupational health services. The Norwegian Data Inspectorate and the Regional Committee for Medical Research Ethics approved this study. All the participating workers gave written informed consent to be included in the study.

All participants were examined by use of questionnaires and neuropsychological tests. The questionnaires were completed under guidance from an occupational physician. The neuropsychological examinations took place during daytime Tuesday to Thursday, after a night's sleep, and took approximately 1.5 hours in total for each participant. The workers had not been exposed to vibrating tools or other physical exposures on the day of

Table 1. Distribution of age, lifestyle factors and other exposure factors retrospectively reported by the group previously exposed to acrylamide and N-methylolacrylamide (NMA) (N=44) and the control group (N=49). [SD=standard deviation.]

Group	Age (years)			Years in construction work		Current smokers				Alcohol consumption ^a		Organic solvent exposure		Previous lead exposure		Vibrating hand-tools		Whole-body vibration	
	Mean	SD	Range	Mean	SD	N	%	Mean ^b	SD	N	%	N	%	N	%	N	%	N	%
Control	44.6	9.7	23–60	19.3	10.7	24	49.0	15.3	5.5	12	24.5	3	6.3 ^c	8	16.3	44	91.7 ^c	25	51.0
Exposed	47.9	9.5	30–70	24.6 ^d	12.5	18	40.9	13.1	6.8	2	4.5	9	20.5	4	9.1	43	97.7	26	60.5 ^d

^a >5 liters pure alcohol per year.^b Number of cigarettes among smokers per day.^c Group size N=48.^d Group size N=43.

the examination. The exposed and control participants were mixed to reduce the risk of systematic errors due to subtle differences in testing methods or equipment over time. The tests were administered without the tester knowing the exposed participants' estimated level of exposure.

Questionnaires on exposure and symptoms

Each participant received questionnaires to examine exposure, background factors, and potential confounders (eg, age, education, current alcohol consumption, current and cumulative smoking habits, previous duration and frequency of work with vibrating hand tools, exposure to organic solvents and several other neurotoxins, and previous injuries). To achieve a standardized overview of retrospectively recalled symptoms during work, we applied a questionnaire consisting of 24 questions covering nervous system symptoms and irritative symptoms related to the skin and mucous membranes, besides some respiratory symptoms. To survey current symptoms, we selected the Q-16 neuropsychiatric questionnaire as it is designed to be short (16 items) but comprehensive on nervous system symptoms relevant to long-term chemical exposure (14, 15). The majority of the Q-16 questions are related to central nervous system function, referring to tiredness, emotional reactions (depression and irritation), problems with memory or concentration, headache and dizziness. In addition, two questions refer primarily to peripheral (difficulties with buttoning or unbuttoning or a tingling sensation in the arms or hands) or autonomous (bodily palpitations, increased perspiration, feeling of oppression in the chest) nervous system function. Two additional questions regarding hand tremor and dizziness were also included.

Exposure assessment

In Norway, 2600 tons of an NMA-based grout (Rhoca-Gil, Siprogel) were used for grouting operations in tunnel construction in the period 1982–97. Based on the number of projects where such grouts had been used,

and the amount of grout used in each project, four construction companies were selected as the study base for the exposed subjects. Approximately half of the amount of NMA-based grout (1300 tons) was used by the four participating construction companies during this period. Workers who had been working in projects where an NMA-based grout had been used for grouting operations were eligible for participation in the study. All study participants allocated to the acrylamide-exposed group confirmed that they had previously been working with grouts containing acrylamide related to injection work.

The NMA/acrylamide-containing grout comprised two solutions, labelled solutions 1 and 2, which were mixed before injection into cracks and crevices in rocks. As the most common work tasks carried out while they were in contact with acrylamide-containing grouts, 30 (71%) workers reported frequent work with mixing solutions 1 and 2, and 32 (74%) reported frequent work with injection work and cleaning of equipment after injection.

The main route of exposure in this study was most likely through dermal contact with the grout and polluted tunnel water, as acrylamide is absorbed via dermal as well as respiratory and oral routes of administration (16). Twenty nine (69%) workers reported frequent spilling of acrylamide on the skin during work with acrylamide in general; 12 (29%) workers reported this occurred only occasionally. In addition, 30 (70%) workers reported frequent spilling of polluted tunnel water on the skin. Despite this, only 12 (28%) workers reported frequent use of raincoats, while 15 (35%) workers claimed never to have used them.

With respect to acrylamide exposure, 15 participants reported 1–6 months exposure, 13 reported 6–24 months, 8 reported 2–4 years, and 6 reported >4 years. We allocated 2 participants who provided no information of exposure duration to the 1–6 months exposure group. The last period of acrylamide/NMA-exposure was reported to be approximately 10 and 3–9 years prior to the examination by 16 and 22 workers, respectively. A further description of the grout and its content of NMA and acrylamide has been presented elsewhere (11).

Neuropsychological examination

As the primary study focus was possible nervous system health effects due to acrylamide exposure, the neuropsychological test battery focused on sensory/motor tests, tests for psychomotor speed, and visually demanding tests. For group comparability reasons, a verbal test and a test for learning and memory of auditory-presented material was included.

The following tests were included in the neuropsychological test battery: Wechsler Adult Intelligence Scale (WAIS) subtests Information, Block Design, and Digit Symbol (17), Halstead-Reitan tests Fingertapping and Grooved Pegboard (18), one test from the computerized NES-2 test battery: Continuous Performance Test (CPT), version 4.5 (Neurobehavioral Systems Inc, Winchester, MA, USA), and an auditory verbal learning test (12 words) with immediate-, interference-, and one-hour delayed recall. CPT measures sustained visual attention. Several different large letters flash briefly (for about 50 msec) on the screen at a rate of one per second for five minutes. The subject presses a button upon seeing an "S" flash on the video display, but not for any other letter. All tests were administered and scored according to standard procedures. Each individual examination took place at the National Institute of Occupational Health (NIOH) neuropsychological test laboratory or in a mobile test laboratory using the same equipment. The two testing sites were equally quiet, and laboratory illumination and the workplace itself were similar.

Statistical analysis

The Statistical Package in the Social Sciences (SPSS) for Windows 17.0 (SPSS Inc, Chicago, IL, USA) was used for data analysis. For the continuous outcome variables in the total sample ($N=93$), we used the Kolmogorov-Smirnov test (19, 20), besides visual inspection of normal probability plots, to assess the normality of variable distribution. Also, variable distribution skewness was calculated. A calculated skewness of 2 was set as the cut-off point for the choice of statistical methods for further data analysis, lower values indicating limited deviation from normal distribution. For skewness above cut-off, group differences were tested with both parametric (independent samples *t*-test) and non-parametric (Mann-Whitney *U* test) methods, rendering only minor differences. Thus, for all continuous measures, arithmetic mean and SD were calculated, and group differences were analyzed with independent samples *t*-tests (table 4). The level of statistical significance was set two-tailed at $P<0.05$. If Levene's Test was significant ($P<0.05$), we corrected for the groups showing different distribution of registrations by applying the corrected values.

Raw scores from WAIS and Halstead-Reitan

subtests were applied in analyses of group differences in neuropsychological test results (table 4). In addition, test raw-scores were converted to T-score equivalents, based on norms corrected for age, gender, and education, developed from a normal population with a defined mean score of 50 and SD 10 (21). These demographically corrected converted scores were used to evaluate group differences in standardized scores on each test, and, secondary, to compare the subgroups of the present study with a normal population and the test results across tests within the present study.

For the dichotomous outcome variables [symptoms during work (table 2) and self-reported current symptoms (table 3)], we used the 2-sided Fisher exact test.

Multiple linear regression analysis, backwards strategy, was chosen to further study the effect of independent variables on neuropsychological test raw-score results in the total group and the exposed and control groups, separately. Age and dichotomous (0–1) variables (i) acrylamide exposure, (ii) exposure to organic solvents (>10 years), (iii) annual alcohol consumption (>5 litres), and (iv) current smoking were included in the model to control for possible confounders (tables 5–6a/6b), while age and all Q-16 questions were included to study the association between self-reported symptoms and neuropsychological test results (table 7). The final models in these analyses were based on an exclusion criterion $P\geq 0.1$ for each covariate.

Results

Symptoms during work, reported 2–10 years post-exposure, are presented in table 2. Compared to the control group, the acrylamide-exposed tunnel construction workers showed significantly higher prevalences of paresthesia in hands and legs, cramps in legs, attacks of white fingers, skin irritation and peeling of skin on the hands, headache, and breathlessness. For other reported symptoms during work, there were no systematic group differences in symptom reporting, although there was a general tendency of higher symptom prevalences in the exposed group.

The response to the neuropsychiatric questionnaire Q-16 on current symptoms also indicated a significantly higher prevalence of complaints among the acrylamide-exposed workers compared to the control group, both regarding tiredness, emotional reactions (depression and irritation), feeling of oppression in the chest, impaired memory and concentration, headache and dizziness, sensory or motor changes (tingling sensation, palpitations), and increased perspiration. Altogether, 25% of the acrylamide-exposed workers claimed having problems with buttoning and unbuttoning. Only the

Table 2. Retrospectively reported symptoms during work in acrylamide and N-methylolacrylamide (NMA) previously exposed group (N=44) and control group (N=49). [PNS=Peripheral Nervous System; CNS=Central Nervous System; ANS=Autonomous Nervous System]

	Exposed group		Control group		P-value ^a
	N	%	N	%	
PNS symptoms					
Paresthesia in hands	24	55.8 ^b	13	27.1 ^c	0.006
Paresthesia in legs	21	48.8 ^b	9	19.1 ^d	0.004
Pain in hands	11	26.8 ^a	10	20.8 ^c	0.618
Pain in legs	10	23.3 ^b	6	12.5 ^c	0.270
Weakness in arms or legs	10	23.3 ^b	7	14.3	0.294
Cramps in legs	14	33.3 ^f	5	10.2	0.009
CNS symptoms					
Headache	25	56.8	13	26.5	0.003
Nausea/dizziness	15	35.7 ^f	8	16.3	0.052
Concentration problems	13	30.2 ^b	7	14.3	0.079
Eye problems when reading	12	27.3	5	10.2	0.058
ANS symptoms					
Sweating, hands	9	20.9 ^b	4	8.2	0.132
Tachycardia	9	20.5	4	8.2	0.134
Diarrhoea	4	9.1	5	10.2	1.000
Voiding problems	4	9.1	3	6.1	0.704
Other symptoms					
Eczema, skin irritation	25	58.1 ^b	16	32.7	0.021
Cough	19	44.2 ^b	17	34.7	0.396
Throat irritation	18	40.9	24	49.0	0.532
Nose irritation	17	39.5 ^b	15	30.6	0.390
Eye irritation	18	41.9 ^b	18	36.7	0.672
Breathlessness	16	36.4	7	14.3	0.017
Wheezing in chest	12	27.3	8	16.3	0.218
Peeling of skin on hands	16	37.2 ^b	3	6.1	0.000
Attacks of white fingers	14	31.8	4	8.2	0.007
Attacks of white toes	3	7.0 ^b	1	2.0	0.336

^a Fisher's exact test (2-sided).^b Group size N=43^c Group size N=48^d Group size N=47^e Group size N=41^f Group size N=42

prevalence of self-reported hand tremor was not significantly elevated (table 3). The median number of reported symptoms was 6.5 (range: 0–17) in the exposed group, and 2.0 (range: 0–11) in the control group, based on all 18 questions set out in table 3.

In contrast, neuropsychological results for the previously exposed group generally did not differ from those of the control group (table 4). Only age- and education-adjusted (21) WAIS Block Design test T-score was significantly higher among the previously acrylamide-exposed, compared to the control group, contrary to a hypothesis of reduced performance due to acrylamide exposure. The auditory verbal learning test (12 words) did not reveal any significant group differences [immediate recall: exposed group mean 5.1 (SD 1.6)

Table 3. Reported current symptoms in previously exposed to acrylamide and N-methylolacrylamide (NMA) group (N=44) and control group (N=49).

	Exposed group		Control group		P-value ^a
	N	%	N	%	
Are you abnormally tired?	24	54.5	11	22.4	0.002
Do you have palpitations even when you are not exerting yourself?	7	16.3 ^b	1	2.0	0.023
Do you often have a painful tingling in some part of your body?	30	68.2	7	14.3	0.000
Do you often feel irritated for no particular reason?	20	45.5	5	10.2	0.000
Do you often feel depressed for no particular reason?	12	27.3	2	4.1	0.003
Do you often have problems concentrating?	16	37.2 ^b	5	10.2	0.003
Do you have a short memory?	29	67.4 ^b	20	40.8	0.013
Do you perspire for no particular reason?	13	29.5	4	8.2	0.014
Do you have any problems with buttoning and unbuttoning?	11	25.0	2	4.1	0.006
Do you generally find it hard to grasp the meaning when reading newspapers and books?	13	30.2 ^b	5	10.2	0.019
Have your relatives told you that you have a short memory?	30	71.4 ^c	18	36.7	0.001
Do you often feel oppression in your chest?	16	38.1 ^c	5	10.2	0.002
Do you have to make notes about what you must remember more often than you think is normal?	15	35.7 ^c	5	10.2	0.005
Do you have to go back and check things you have done, such as turned off the stove, locked the door, etc?	27	62.8 ^b	17	34.7	0.012
Do you have a headache at least once a week?	15	35.7 ^c	7	14.3	0.026
Are you less interested in sex than you think is normal?	7	16.7 ^c	1	2.0	0.022
Do you experience frequent dizziness?	11	25.6 ^b	0	0.0	0.000
Do you often have tremor in your hands	10	23.3 ^b	6	12.2	0.181

^a Fisher's exact test (2-sided).^b Group size N=43^c Group size N=42

words versus the control group mean 5.6 (SD 1.7), $P=0.16$; maximum number of words recalled in one trial: exposed group mean 11.0 (SD 1.4) versus control group mean 11.1 (SD 1.2), $P=0.64$; and one hour delayed recall: exposed group mean 9.2 (SD 2.5) versus control group mean 9.5 (SD 1.9), $P=0.48$].

When age and other potential confounders were

Table 4. Neuropsychological test results in previously acrylamide and N-methylolacrylamide (NMA) exposed (N=44) and control (N=49) groups. [SD=standard deviation; 95% CI=95% confidence interval; WAIS=Wechsler Adult Intelligence Scale. NES2-CPT=Neurobehavioral Evaluation System Continuous Performance Test.]

	Test raw scores								Test T-scores ^a							
	Exposed		Control		Difference		P-value ^b		Exposed		Control		Difference		P-value ^b	
	Mean	SD	Mean	SD	Mean	95% CI of difference			Mean	SD	Mean	SD	Mean	95% CI of difference		
WAIS Information (points)	16.0	4.3	16.4	3.9	0.4	-1.3–2.1	0.653		50.1	10.4	48.8	10.2	-1.4	-5.6–2.9	0.519	
WAIS Digit Symbol (number of responses)	43.0	12.8	43.6	9.8	0.6	-4.1–5.3	0.795		48.5	7.3	47.0	6.4	-1.5	-4.4–1.3	0.289	
WAIS Block Design (points)	33.4	9.1	31.7	7.3	-1.7	-5.1–1.6	0.310		51.0	10.3	46.9	8.2	-4.1	-7.9– -0.2	0.037	
Fingertapping, right hand (number of responses)	48.7	9.9	51.7	7.2	3.0	-0.5–6.6	0.092		47.6	12.7	51.2	10.5	3.6	-1.1–8.4	0.135	
Fingertapping, left hand (number of responses)	43.4	7.5	46.2	5.3	2.8	0.1–5.4	0.043		44.6	10.9	48.5	9.3	4.0	-0.2–8.1	0.062	
Grooved Pegboard, right hand (sec)	78.3	16.0	79.1	17.7	0.8	-6.2–7.8	0.823		45.5	9.6	43.7	9.5	-1.8	-5.8–2.1	0.364	
Grooved Pegboard, left hand (sec)	87.2	17.6	88.7	16.8	1.5	-5.6–8.6	0.682		41.0	8.6	38.0	8.7	-3.0	-6.5–0.6	0.104	
NES2-CPT ^c (msec)	416.1	60.8	398.4	39.3	-17.7	-38.5–3.2	0.096		.	.	.	.	.	.	.	.

^a Converted from raw scores, using previously developed normal population norms correcting for age, gender and education, Heaton (21).

^b Independent samples t-test, two-tailed.

^c Heaton T-scores not available.

included in a linear regression model, as expected, age was a significant determinant for several of the neuropsychological outcome measures in the total group. Acrylamide exposure did not contribute to the model for any of the tests, while self-reported annual alcohol consumption (>5 litres) contributed to reduced fine motor coordination (table 5). In the acrylamide-exposed group, cigarette smoking was a consistent, but not statistically significant, determinant for reduced performance on motor tests Fingertapping, Pegboard left hand, and CPT (table 6a).

We further examined the relation between some neuropsychological tests, and all Q-16 questions, including the questions about hand tremor and dizziness, in the acrylamide-exposed and control group, respectively (table 7). Age seemed to be more important among the acrylamide-exposed than the control group in predicting the motor test results. In addition, self-reported hand tremor was a predictor for reduced performance on Fingertapping and Grooved Pegboard in the acrylamide-exposed but not in the control group.

Discussion

The results from the present study show that retrospectively evaluated symptom prevalence during tunnel work was high in the group of tunnel workers previously exposed to acrylamide and NMA during grouting work, in particular regarding paresthesia in hands and

legs, headache, and skin irritation. Also, the prevalence of current symptoms from the Q-16 questionnaire was significantly higher among the exposed, compared to the control group. In contrast, no relationship between occupational acrylamide exposure and neuropsychological test results was observed.

Several methodological issues need to be addressed in this cross-sectional study design. One problem is related to the representativeness of our studied population. Selection into a study may influence the study outcome, but high participant rate makes selective participant dropout from both groups unlikely in our study.

Questionnaire-based symptom registration reflects by definition subjective perception, not objective reality. It is well known that besides the content of the questions, a variety of factors of both psychological (general social) and situational origin, and even factors related to the mere construction of questionnaires, may affect questionnaire responses (15). Biases may also be related to both an effect of being studied, or to the perception or interpretation of consequences of the research (22, 23).

Of particular relevance to the present study, is that an association between self-reported symptoms during work and self-reported exposure may occur due to collection of the two data-categories using similar methods (common method bias). Recall bias in either temporal direction is likely to create an association between current symptoms and past exposure. Current symptoms may lead to an over-estimation of past exposure or symptoms during work, while previous high exposure

Table 5. Neuropsychological test results as a function of age, acrylamide exposure and lifestyle factors in previously acrylamide and N-methylolacrylamide (NMA) exposed group and control group together (N=93). Backwards linear regression: acrylamide/ N-methylolacrylamide exposure, age, exposure to organic solvents, alcohol consumption > 5 l/year, and smoking included in model. [B=B-coefficient; WAIS=Wechsler Adult Intelligence Scale; NES2-CPT=Neurobehavioral Evaluation System Continuous Performance Test.]

Raw scores	Regression coefficients ^a									R ²	Model P-value	
	Constant ^b		Age		Acrylamide exposure		Smoking		Alcohol			
	B		B	P-value	B	P-value	B	P-value	B			P-value
WAIS Information (points)	16.3		.	.	.	.	.	.	.	.	0.00	.
WAIS Digit Symbol (number of responses)	76.8		-0.7	<0.001	.	.	.	.	.	.	0.39	<0.001
WAIS Block Design (points)	51.5		-0.4	<0.001	3.0	0.049	.	.	.	.	0.27	<0.001
Fingertapping, right hand (number of responses)	67.8		-0.4	<0.001	.	.	.	.	.	.	0.18	<0.001
Fingertapping, left hand (number of responses)	59.4		-0.3	<0.001	.	.	.	.	.	.	0.22	<0.001
Grooved Pegboard, right hand (sec)	44.5		0.7	<0.001	.	.	.	.	11.1	0.016	0.19	<0.001
Grooved Pegboard, left hand (sec)	45.3		0.8	<0.001	.	.	5.7	0.077	8.5	0.062	0.24	<0.001
NES2-CPT, mean (msec)	322.5		1.8	0.001	.	.	.	.	.	.	0.12	0.001

^a B-coefficient (referring to raw scores for each test) shown for variables included in the final model, exclusion criterion P>=0.100.

^b P<0.001 for all dimensions.

may be associated with reduced threshold for reporting of current symptoms. We interpret the high prevalence of self-reported symptoms among the exposed workers in this study compared to the controls, (tables 2 and 3) to be at least partly due to such systematic errors.

Public attention on the possible health effects of acrylamide exposure at the time of the study health examinations may also have influenced the level of symptom reporting and strengthened a possible recall bias.

In contrast, the neuropsychological test results are considered less vulnerable to information bias. However, a potential expectation bias may be considered, as the neuropsychologist was not sufficiently blinded as to whether the participants belonged to the exposed or control group. The absence of group differences in neuropsychological test results, however, does not indicate that inadequate blinding has contributed to any expectation bias in the present study.

No acrylamide measurements were performed in the tunnel projects where the exposed workers had been employed. Half-life for acrylamide is approximately 2 hours in blood, and 5 hours in tissue (24). Biomonitoring of hemoglobin adduct levels of acrylamide in blood provides comprehensive information about the amount of acrylamide entering a person's body during the preceding months only, with a critical time window of up to 4 months, related to the approximately 120 days average life span of the erythrocytes (9, 25). Consequently, biomonitoring of exposure was not possible due to the retrospective study design, examining participants >2 years post-exposure. In the absence of objective exposure indicators, we asked each worker about work tasks, exposure conditions, and duration of exposure. Neuropsychological

test results showed no systematic association with self-reported exposure duration. Unfortunately, the exposure duration question was ambiguous and did not make a clear distinction between active time spent with tasks where exposure might take place, and time spent in projects where acrylamide has been applied regardless of individual exposure conditions. Since this information was partly recalled from tunnel projects far back in time, we chose a dichotomous exposure categorization in the analyses, as the exposure information was not considered detailed enough to create any reliable exposure surrogate for an individual "dose".

Substituting the dichotomous exposure variable with an exposure-intensity index, based on the participants' qualitative information about exposure conditions, did not alter exposure-effect relationship considerably and is not reported.

In addition, the time dimension was not sufficiently stated in the questionnaire for the question covering symptoms *during work* (table 2). We anticipate that the acrylamide-exposed group reported symptoms during previous acrylamide-exposed work (ie, >2 years prior to the health examination), while the controls may have included symptoms both during past and present work. The potentially different time windows for reporting symptoms "during work" complicate the interpretation of these data.

Five workers in our present study, reporting their last exposure roughly two years prior to the examination, might theoretically have reduced test performance due to incomplete recovery, rather than a potential permanent effect. Comparison of the test results of these workers with age-matched controls, gave no indications of

Table 6a. Neuropsychological test results in previously acrylamide and N-methylolacrylamide (NMA) **exposed group** (N=44). Backwards linear regression: age, exposure to organic solvents, alcohol consumption (>5 l/year), and smoking included in model. [B=B-coefficient; WAIS=Wechsler Adult Intelligence Scale; NES2-CPT=Neurobehavioral Evaluation System Continuous Performance Test.]

Raw scores	Exposed group, regression-coefficients ^a								R ²	Model P-value
	Constant		Age		Solvents	Smoking		Alcohol		
	B	P-value	B	P-value		B	P-value			
WAIS Information (points)	16.0	<0.001	.	.	.	.	.	.	0.00	.
WAIS Digit Symbol (number of responses)	81.9	<0.001	-0.8	<0.001	.	.	.	.	0.37	<0.001
WAIS Block Design (points)	57.9	<0.001	-0.5	<0.001	.	.	.	.	0.29	<0.001
Fingertapping, right hand (number of responses)	72.7	<0.001	-0.5	0.002	.	-5.2	0.060	.	0.25	0.003
Fingertapping, left hand (number of responses)	64.6	<0.001	-0.4	<0.001	.	-3.5	0.084	.	0.31	<0.001
Grooved Pegboard, right hand (sec)	43.8	<0.001	0.7	0.004	.	.	.	.	0.18	0.004
Grooved Pegboard, left hand (sec)	32.0	0.008	1.1	<0.001	.	7.5	0.095	.	0.38	<0.001
NES2-CPT (mean msec)	302.3	<0.001	2.1	0.026	.	30.5	0.088	.	0.16	0.027

^a B-coefficient (referring to raw scores for each test) shown for variables included in the final model, exclusion criterion P>=0.100.

Table 6b. Neuropsychological test results in previously acrylamide and N-methylolacrylamide (NMA) **control group** (N=49). Backwards linear regression. Age, exposure to organic solvents, alcohol consumption (>5 l/year), and smoking included in model. [B=B-coefficient; WAIS=Wechsler Adult Intelligence Scale; NES2-CPT=Neurobehavioral Evaluation System Continuous Performance Test.]

Raw scores	Control group, regression-coefficients ^a								R ²	Model P-value	
	Constant ^b		Age		Solvents		Smoking	Alcohol			
	B		B	P-value	B	P-value		B			P-value
WAIS Information (points)	16.5	.	.	.	.	.	.	.	0.00	.	
WAIS Digit Symbol (number of responses)	73.9	-0.7	<0.001	.	.	.	.	.	0.44	<0.001	
WAIS Block Design (points)	48.6	-0.4	<0.001	.	.	.	.	.	0.26	<0.001	
Fingertapping, right hand (number of responses)	64.8	-0.3	0.006	.	.	.	.	.	0.15	0.006	
Fingertapping, left hand (number of responses)	54.9	-0.2	0.007	5.9	0.044	.	.	.	0.22	0.004	
Grooved Pegboard, right hand (sec)	48.2	0.6	0.015	.	.	.	11.3	0.045	0.19	0.009	
Grooved Pegboard, left hand (sec)	63.8	0.6	0.027	.	.	.	.	.	0.10	0.027	
NES2-CPT (mean msec)	333.7	1.4	0.014	.	.	.	.	.	0.13	0.014	

^a B-coefficient (referring to raw scores for each test) shown for variables included in the final model, exclusion criterion P>=0.100.

^b P<0.001 for all dimensions.

incomplete recovery. In addition, a group of recently NMA-exposed workers showed close to complete peripheral nerve recovery compared to a control group, 16 months post-exposure (11).

When comparing the crude profile of the symptoms reported during work in our study to previous studies among tunnel workers with recent NMA exposure (9, 11), all studies reported an elevated prevalence of symptoms known to be associated with acrylamide exposure, such as paresthesia in hands and legs, skin irritation and peeling of skin on hands. Although symptom prevalence is particularly vulnerable to differential criteria for inclusion in the studies, NMA-exposure has probably been comparable in the three studies, considering both general working conditions and symptom profiles among workers during work.

For comparability reasons, we chose another group of tunnel workers as a reference group. This was an advantage in most group comparisons – the participants of both groups were tunnel construction workers, indicating generally similar work, occupational exposure,

and health risks. In addition, their mean duration of education is close to identical, and their neuropsychological test results on general verbal test in particular do not indicate systematic cognitive differences.

As the participants in the previously exposed group had been involved in tunnel projects many years ago, we did not succeed in complete age-matching between the two groups, thus, the exposed group were on average 3.3 years older than the controls. As most of our chosen neuropsychological outcome parameters are age-related (21), age was included and adjusted for in all analyses involving neuropsychological test results. Of the previously exposed workers, 11 were out of work at the time of examination: 3 were retired due to older age, 1 was unemployed, 6 were on sick leave, and 1 received disability pension, all of them due to conditions unrelated to the outcomes of our study (ie, asthma, hyperthyroidism, suspected coronary disease, elevated blood pressure, and musculoskeletal problems with normal neurography). The neuropsychological test results did not differ significantly between these subjects and the rest of the exposed group.

Table 7. Motor manual neuropsychological test results as a function of age and current subjective symptoms according to Q16-questionnaire, in previously acrylamide and N-methylolacrylamide (NMA) exposed group (N=44) and control group (N=49) separately. Backwards linear regression: age and Q-16-symptoms included in model.

	Test raw score ^a							
	Exposed group				Control group			
	Fingertapping, right hand (number of responses) ^b	Fingertapping, left hand (number of responses)	Grooved pegboard, right hand (sec)	Grooved pegboard, left hand (sec)	Fingertapping, right hand (number of responses) ^c	Fingertapping, left hand (number of responses) ^d	Grooved pegboard, right hand (sec)	Grooved pegboard, left hand (sec)
Constant								
B-coefficient	70.2	63.3	42.0	26.8	63.9	55.4	52.6	60.9
P-value	<0.001	<0.001	<0.001	0.017	<0.001	<0.001	<0.001	<0.001
Age								
B-coefficient	-0.5	-0.4	0.7	1.1	-0.3	-0.2	0.6	0.7
P-value	0.001	0.001	0.004	<0.001	<0.009	0.013	0.023	0.006
Hand tremor								
B-coefficient	-17.7	-7.6	16.1	.	.	.	.	.
P-value	<0.001	0.002	0.003	.	.	.	.	.
Depressed								
B-coefficient	-14.0	.	.	.	.	.	.	.
P-value	0.001	.	.	.	.	.	.	.
Oppression in the chest								
B-coefficient	.	.	.	.	.	.	.	-18.9
P-value	.	.	.	.	.	.	.	0.013
Abnormally tired								
B-coefficient	.	.	.	10.5	.	-4.0	.	.
P-value	.	.	.	0.016	.	0.016	.	.
Headache weekly								
B-coefficient	6.9	.	.	.	.	.	.	.
P-value	0.021	.	.	.	.	.	.	.
Palpitations								
B-coefficient	-10.4	.	.	.	.	.	.	.
P-value	0.006	.	.	.	.	.	.	.
Subnormal interest in sex								
B-coefficient	14.6	.	.	.	.	.	.	.
P-value	0.002	.	.	.	.	.	.	.
Check things								
B-coefficient	9.5	.	.	.	.	.	.	.
P-value	0.004	.	.	.	.	.	.	.
R ²	0.68	0.44	0.39	0.50	0.23	0.28	0.11	0.22
Model P-value	<0.001	<0.001	<0.001	<0.001	0.008	0.002	0.023	0.004

^a B-coefficient (referring to raw scores for each test) shown for variables included in the final model, exclusion criterion $P \geq 0.100$.

^b Concentration (-6.4, $P=0.056$), Oppression in chest (5.0, $P=0.088$), Take notes to memorize (4.9, $P=0.086$), also contribute to the model.

^c Concentration (-6.3, $P=0.063$), Oppression in chest (6.4, $P=0.060$), also contribute to the final model.

^d Depression (-6.6, $P=0.059$) also contribute to the final model.

As they were all exposed to various substances during work, which may influence health and performance, we presented test raw scores and demographically corrected converted t-scores based on norms stratified according to age, gender, and education, to enable comparison with a relevant normal population. The tunnel workers showed a performance on cognitive tests within the normal distribution of the comparable general population, while there was a tendency of slightly reduced performance (1.0 SD below mean) on some sensorimotor manual tests (Grooved Pegboard).

Heavy smoking (26, 27) and alcohol consumption (28) may influence the nervous system. Increased tremor has been found among smokers or snufflers compared

to non-smokers/non-snufflers (29). Cigarette smoking is also a source of acrylamide exposure (30-32), although acrylamide neurotoxicity due to smoking alone is not clinically relevant (32). The proportion of current smokers was comparable in the two groups. Annual alcohol consumption (>5 litres) was more frequent among the controls, while exposure to organic solvents was more frequent among the previously exposed group. These covariates were included into the regression analyses.

Most workers reported working with vibrating hand tools, a slightly higher proportion among the exposed than the control group (98% and 92%, respectively). None of the workers had been using such tools on the day of the health examination. In a previous study,

vibration-sensitive outcomes such as distal delay, sensory conduction velocities, and amplitudes of the ulnar and median nerves were found to be comparable in the two groups (12), thus not indicating a systematic difference in acute or persistent nerve function of the arms. The data accordingly do not support a hypothesis that the excess of sensory symptoms in the exposed group could be explained by differences in work with vibrating tools.

The absence of group differences on neuropsychological testing (and no pattern of systematic contribution from acrylamide-exposure or smoking to explain the variance in neuropsychological test results in the total sample) indicates no or limited persisting effects from acrylamide- and NMA-exposure on neurobehavioral outcome measures. However, the discrepancy between the positive results based on self-reporting and the non-positive neuropsychological test results needs to be further considered. Functional domains assessed by questionnaires are not necessarily consistent with similar functions assessed by neuropsychological testing in the same person. This has recently been demonstrated in a study of self-reported memory problems and memory problems as defined by neuropsychological testing (33), pinpointing the view that asking people about health problems is not sufficient.

However, in spite of limitations related to the use of subjective information, we cannot completely disregard self-reported symptoms as indicators of "true" health effects, as the applied neuropsychological tests may not have covered functions making them valid indicators of nervous system effects due to occupational acrylamide exposure. We have recently identified possible visual system CNS effects in this group of previously acrylamide- and NMA-exposed workers (12, 13).

The separate exposed and control group analysis of effect from different exposures on neuropsychological test results was chosen to investigate whether such comparison could reveal subtle differences in response to these exposures as a function of the previous NMA-exposure. Dietary intake and smoking habits are well-known sources of acrylamide exposure. Thus, the reduced fine motor speed and coordination in the exposed group only could reflect an effect due to a combination of dietary acrylamide, cigarette smoking, and occupational exposure. However, the low statistical power of the study makes the observations inconclusive.

The observed association between self-reported hand tremor and the neuropsychological tests Fingertapping, and Pegboard right hand, in the acrylamide-exposed group must also be considered inconclusive regarding an exposure-effect association, due to the non-positive result regarding group differences between the acrylamide-exposed and control groups on these tests.

The non-positive neuropsychological results in the present study may also be related to the limited sample size in this study. The power of the present study is 0.65 for an effect size of 0.5 SD reduced performance based on the raw score values (mean/SD) of the control group. Based on the above considerations, a power of 0.80 would require a group size of approximately $N=65$, which was not possible to achieve, considering the limited number of eligible subjects with relevant exposure. The absence of neuropsychological test group differences must accordingly be considered non-positive rather than true negative results, as there may theoretically be a true group difference, which is blurred due to limited study groups.

Concluding remarks

Despite high prevalences of self-reported current symptoms in the acrylamide-exposed group, we did not find an association between occupational acrylamide exposure and health outcomes as measured by the chosen neuropsychological tests. Observed associations between chemical exposure and self-reported symptoms should be interpreted with great caution.

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