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Knowledge compilation

The influence of chemical substances on cognitive functions in working life

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Knowledge compilation

The influence of chemical substances on cognitive functions in working life

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Innehåll

Preface

The Swedish Work Environment Agency has published a number of knowledge compilations written by renowned researchers, presenting the state of knowledge in various fields. All knowledge compilations can be downloaded for free from the web site of the Swedish Work Environment Agency. The web site also offers films and presentations from seminars organised by the Swedish Work Environment Agency in connection to the publication of knowledge compilations.

The report was reviewed by Lars-Gunnar Gunnarsson, Professor at School of Medical Sciences, Örebro University and retired physician in Neurology, and Environmental and Occupational Medicine. The final version of the report is the responsibility of the authors themselves.

Project leader for this knowledge compilation at the Swedish Work Environment Agency was Carin Håkansta. We would also like to thank other colleagues at the Swedish Work Environment Agency who assisted in developing the report.

Views expressed in this knowledge compilation belong to the authors and do not necessarily reflect the views of the Swedish Work Environment Agency.

Ann Ponton Klevestedt

Head of statistics and analysis

Swedish Work Environment Agency

Summary

The use of neurotoxic substances in Swedish work-life, as well as the exposure levels to these substances, have decreased significantly over time thanks to improved hygienic conditions. However, several chemical substances that occur in Swedish work-life are neurotoxic and may, at sufficiently high exposure levels, affect the brain's cognitive functions. High, short-term exposure may cause acute symptoms that can be observed clinically. However, even relatively low exposure levels may cause subtle effects on neuropsychological functions, and, in the long-term, permanently impair cognitive abilities.

The aim of this knowledge compilation is to present and analyse existing knowledge from international research on work-related exposures to chemical substances and their effects on neuropsychological functions. Another aim is to indicate how this knowledge applies to Swedish working conditions, and thus contribute to improved prevention. A third aim is to make the knowledge more accessible to employers and others who work with health and safety issues and thereby spread knowledge and raise awareness of these issues.

A systematic literature research was performed using PubMed. The search string included exposure terms for seven selected neurotoxic substances (aluminium, lead, manganese, inorganic mercury, solvents, carbon monoxide, and hydrogen sulphide) and outcome terms related to neuropsychological functions, and terms for different neuropsychological tests. Only studies with N>10 participants which applied neuropsychological methods were included. Further, the studies had to include either a control or comparison group, or a differentiation of exposure, or comparison with established norms to be included. The findings from the included studies were analysed according to the tested neuropsychological domains and the outcomes were classified using a simplified scoring system. Adjustments for sex had been done in some of the studies, but not in all, so in this report the results were not stratified for women and men in this report.

Several studies included tests for **attention/working memory,** but no clear tendency was observed. For the metals, roughly half of the studies reported at least one test result where this function was affected. Among the studies of patients with solvent-induced encephalopathy and the carbon monoxide studies, the majority of the studies reported problems with these functions.

Speed of information processing, the ability to perform simple repetitive cognitive tasks quickly and fluently, is affected in many diseases affecting the central nervous system. For most of the exposures, a tendency towards slower information processing was found, and the strongest effect was found among subjects exposed to manganese and carbon monoxide.

Executive function was assessed in a limited number of studies, in which the positive results/findings seemed to outnumber the negative ones. However, there was one exception to this: the effect was not found for the mercury studies.

Spatial skills/perceptual organization: 10 out of 16 studies of lead exposure and 8 out of 13 studies of mercury exposure reported an effect. Also, in the CO studies, the three studies that included this function reported an effect. As this function is a central factor in the person's intelligence, there is a possibility that difference between groups regarding this function, might indicate that the groups were not matched well regarding intellectual function.

Verbal/academic skills are central elements of a person's general intelligence, and are often tested to ensure that the groups under study are well matched. Differences between these functions may indicate that the groups are not matched well in terms of intellectual function.

In the studies of aluminium and solvents, and, to a certain degree, lead, most studies were negative, while for the other exposures there were about as many positive as negative findings.

Verbal memory was assessed in a limited number of studies, probably because these tests tend to be time consuming. The majority of studies of lead produced positive results, while for aluminium and solvents more negative than positive findings were observed.

For **visual memory** no clear effect was found, for most studies there were as many positive as negative findings, with a tendency towards more negative findings in the studies of mercury.

Reaction time was negative in eight out of eleven studies of mercury where tests of reaction time were applied. For the other exposures, there were about as many negative as positive findings.

Tests for **manual dexterity/manual speed** have been applied in a number of studies. Three of the four metals: lead, manganese and mercury, reported impaired manual dexterity/manual speed in a majority of the studies. This was not so for aluminium or for solvents, where there was a tendency towards more negative findings.

Tremor was reported in a majority of the studies of manganese and mercury. One study of lead included a tremor test, and yielded a positive finding. Two out of seven studies of aluminium were positive, while the two solvent studies where tests for tremor were applied did not report any effects on tremor.

Regarding **other Motor skills,** such as grip strength or hand-eye coordination, the positive studies outnumbered the negative ones in studies of manganese and lead while no clear tendency was found for the other exposures.

Symptoms/Diagnosis of cognitive impairment. In the studies where a symptom questionnaire was included, with one exception (CO), the positive findings outnumbered the negative ones.

In summary, these neurotoxic substances may cause subtle long-term effects on various neuropsychological domains, even if no detectable effects on an individual basis are to be expected following exposure in normal working conditions. Thus, preventive work is necessary for eliminating or reducing risks to the greatest extent possible. Systematic work environment management is an important tool for employers. Employees can be protected by means of education, support and guidance, or personal protective equipment. Hygiene conditions can be monitored by measurements performed at the workplace and biological monitoring. Some exposures (i.e. H_2S and CO) may cause severe effects at short-term high exposures. In these cases, use of real-time personalized measurement equipment carried by workers may identify peak exposures. A growing foetus will generally be very sensitive to neurotoxic substances and therefore a risk assessment must be performed whenever pregnant or nursing women are at risk of being exposed to neurotoxic substances of any kind.

Sammanfattning på svenska

Användningen av neurotoxiska substanser i svenskt arbetsliv, liksom exponeringsnivåerna för dessa ämnen, har minskat betydligt över tid på grund av förbättrade hygieniska förhållanden. Dock förekomme flera kemiska substanser i svenskt arbetsliv som är neurotoxiska och som vid tillräcklig höga exponeringsnivåer kan påverka hjärnans kognitiva funktioner. Hög och kortvarig exponering kan orsaka akuta symtom som kan observeras kliniskt. Dock kan även relativt låga exponeringsnivåer orsaka subtila effekter på neuropsykologiska funktioner, och på lång sikt permanent försämring i kognitiva förmågor.

Syftet med denna kunskapssammanställning är att presentera och analysera befintlig kunskap från internationell forskning om arbetsrelaterade exponeringar för kemiska substanser och deras effekter på neuropsykologiska funktioner. Ett annat syfte är att ange hur denna kunskap kan tillämpas på svenska förhållanden i arbetslivet och därmed bidra till förbättrad prevention. Ett tredje syfte är att göra kunskapen mer tillgänglig för arbetsgivare och andra kategorier som arbetar med hälso-och säkerhetsfrågor och därigenom sprida kunskap och öka medvetenheten om dessa frågor.

En systematisk litteratursökning utfördes med hjälp av PubMed. Söksträngen inkluderade termer gällande exponering för sju utvalda neurotoxiska substanser (aluminium, bly, mangan, oorganiskt kvicksilver, lösningsmedel, kolmonoxid och vätesulfid), och utfall i termer relaterade till neuropsykologiska funktioner och olika neuropsykologiska test. Endast studier med N> 10 deltagare som tillämpade neuropsykologiska metoder och inkluderade en kontroll-eller jämförelsegrupp eller differentiering av exponering, eller jämförelse med etablerade normer inkluderades. Resultaten från de inkluderade studierna analyserades utifrån vilka neuropsykologiska domäner som testades och klassificerades sedan med hjälp av ett förenklat poängsystem. Justering för kön hade gjorts i en del av studierna, därför har det inte varit möjligt att redovisa resultaten separat för kvinnor och män i denna rapport.

Flera studier inkluderade tester för **uppmärksamhet/arbetsminne,** men ingen tydlig tendens observerades. Avseende metallerna rapporterade ungefär hälften av studierna minst ett testresultat där denna funktion var påverkad. Majoriteten av studierna av patienter med lösningsmedelsinducerad encefalopati och kolmonoxidstudierna, rapporterade problem med dessa funktioner.

Snabbhet i informationsbearbetning, förmågan att utföra enkla repetitiva kognitiva uppgifter snabbt och flytande, är försämrad vid många sjukdomar som påverkar centrala nervsystemet. För de flesta exponeringarna sågs en tendens till långsammare

informationsbearbetning, och den starkaste effekten sågs bland personer som var exponerade för mangan och kolmonoxid.

Exekutiva funktioner bedömdes i ett begränsat antal studier. I de studier där sådana tester tillämpades, tenderade positiva resultat/fynd att vara fler än de negativa med ett undantag; någon effekt sågs inte i kvicksilverstudierna.

Spatial förmåga/perceptuell organisation: det rapporterades en effekt på denna funktion i 10 av 16 studier gällande exponering för bly, och i 8 av 13 av kvicksilverstudierna. Även i kolmonoxidstudierna rapporterades en effekt i de tre studier där funktionen inkluderades. Eftersom denna funktion är en central faktor i en persons intelligens, finns det en möjlighet att en påvisad skillnad mellan olika grupper i denna funktion, beror på att dessa inte var väl matchade avseende intellektuell förmåga.

Språkliga funktioner är centrala inslag i en persons allmänna intelligens, och testas ofta för att se till att de grupper som studeras är väl matchade. Skillnader i dessa funktioner kan tyda på att grupperna inte är väl matchade avseende intellektuell funktion. I studierna av aluminium och lösningsmedel, och till en viss grad bly, var de flesta studierna negativa, medan det fanns ungefär lika många positiva som negativa fynd för de övriga exponeringarna.

Det **verbala minnet** bedömdes i ett begränsat antal studier, förmodligen eftersom dessa tester tenderar att vara tidskrävande. I majoriteten av studierna av bly påvisades positiva fynd, medan det för aluminium och lösningsmedel observerades fler negativa än positiva fynd.

För **visuellt minne** fanns ingen tydlig effekt; i de flesta studierna fanns det lika många positiva som negativa fynd, med en tendens till fler negativa fynd i studierna av kvicksilver.

Reaktionstiden visade ingen påverkan i åtta av elva studier av kvicksilverexponering, där det ingick tester av reaktionstiden. För de övriga exponeringarna fanns det ungefär lika många negativa som positiva fynd.

Tester för **manuell fingerfärdighet/manuell hastighet** har tillämpats i ett antal studier. För tre av de fyra metallerna; bly, mangan och kvicksilver, rapporterades nedsatt manuell fingerfärdighet/manuell hastighet i en majoritet av studierna. Det var inte fallet för aluminium eller lösningsmedel, där det fanns en tendens till övervägande negativa fynd.

Tremor rapporterades i en majoritet av studierna av mangan och kvicksilver. En studie av bly hade inkluderat ett tremor test, och med ett positivt fynd. I två av sju studier av aluminium angavs positiva fynd, medan det inte rapporterades några effekter på tremor i de två lösningsmedelsstudierna, där tester för tremor tillämpades.

När det gäller **andra motoriska färdigheter,** såsom greppstyrka eller hand-öga-koordination, var antalet positiva fynd fler än de negativa i studierna av mangan och bly, men någon tydlig tendens konstaterades inte för de övriga exponeringarna.

Symtom/diagnos av kognitiv svikt. I de studier där ett symptomfrågeformulär ingick var de positiva fynden fler än de negativa med undantag för kolmonoxid.

Sammanfattningsvis kan dessa neurotoxiska substanser orsaka subtila långtidseffekter på olika neuropsykologiska domäner, även om några påvisbara effekter på individuell basis inte kan förväntas efter exponering vid normala arbetsförhållanden. Att arbeta förebyggande är därför nödvändigt för att eliminera eller minska riskerna så långt som möjligt. Det systematiska arbetsmiljöarbetet är ett viktigt verktyg för arbetsgivaren i detta arbete. De anställda kan skyddas genom utbildning, stöd och vägledning, eller personlig skyddsutrustning. Hygieniska förhållanden kan övervakas genom mätningar på arbetsplatsen och biologisk övervakning. Vissa exponeringar (dvs. vätesulfid och kolmonoxid) kan leda till mycket allvarliga effekter vid kortvariga höga exponeringar. I dessa fall kan användning av personlig mätutrustning i realtid som bärs av arbetstagarna identifiera eventuella toppexponeringar. Det växande fostret är generellt mycket känsligt för neurotoxiska substanser. Därför måste en riskbedömning alltid göras när gravida och ammande kvinnor riskerar att utsättas för neurotoxiska substanser av något slag.

1. Introduction

Background

Many of the chemical substances that occur in working life are neurotoxic and can, at sufficiently high exposure levels, affect the brain's cognitive functions, e.g., the ability to plan and organize, attention, memory, speed in information processing, and verbal and spatial skills. High, short-term exposure may cause acute, usually transient symptoms. In the case of repeated or prolonged exposure, the likelihood of permanent cognitive impairment will increase. However, even relatively low exposure levels may have subtle effects on neuropsychological function, and, in the long term, permanently impair cognitive capacity.

A reduction of cognitive capacity implies significant problems at a time when cognitive and emotional demands in working life continue to increase. Moreover, a reduction of cognitive and emotional ability may lead to increased vulnerability to exhaustion and conflicts, for example. Thus, early detection of adverse effects on brain function is of great importance, as is the development of preventive strategies. The earliest signs of neurotoxic effects may differ between chemical substances and classes of substances. Some chemical substances may negatively affect the brain of the growing foetus, and thus affect the next generation.

Employers usually get information from safety data sheets that give occupational exposure limit values. Occupational exposure limit values are based on scientific documentation that comprises all adverse effects, including effects on the central nervous system (CNS), assuming such data is available.

For example, detailed knowledge about particular chemical substances and their effects on the CNS, including effects on neuropsychological functions, is available in evaluation documents published by the Swedish criteria group, the Nordic Criteria group, and the EU's SCOEL Expert Committee. Information is also available in medical data bases, among others, the EU's Chemicals Agency ECHA. There is presently a lack of easily accessible information regarding the effects of chemical substances on neuropsychological functions.

Aim

The first aim of this compilation of knowledge is to present and analyse existing knowledge from international research on work-related exposures to chemical substances and their effects on neuropsychological functions. A second aim is to indicate how this knowledge can be applied to Swedish working conditions, and thus contribute to improved prevention. A third

aim is to make the knowledge more accessible to employers and others who work with health and safety issues and thereby raise knowledge and awareness of these issues.

Target group

The target group for the knowledge compilation is everyone who works with this type of work environment issues; primarily, these are employers, safety officers, and personnel in the occupational health service. Knowledge compilations are also an important source of competence development for the Swedish Work Environment Authority's own staff, at the inspection department, the regulatory department and the response service.

Outline of the report

This knowledge compilation is based on a broad search of international and national research on the cognitive effects of chemical exposures. The present study comprises neuropsychological effects associated with occupational exposure to the metals aluminium, lead, inorganic mercury and manganese, as well as some other substances such as carbon monoxide, hydrogen sulphide, and mixed solvents.

Common research methods used for detection of cognitive effects and a description of the neuropsychological concepts used in the report are presented in chapter 3. This terminology relies on the neuropsychological functions presented in a previous report, with some modifications (Karlsson et al. 2014).

In chapter 4, we present the results of the literature search for the various substance groups or substances. For some exposures, differences in sensitivity according to gender or age as well as the impact on the next generation are discussed. The results are presented in tables based on the cognitive domains described in the neuropsychological methods section. In chapter 5, a brief summary of the findings related to each cognitive domain are presented. In chapter 6, validity aspects are discussed. In chapter 7, the consequences of knowledge and knowledge gaps, as well as preventive aspects, are discussed.

Rita Bast-Pettersen has written chapters 2 (Methods), 3 (Neuropsychological domains/functions), 4.1 (Aluminium), 4.3 (Manganese), 4.6 (Organic solvents) and 6 (Aspects of validity), and Gunilla Wastensson chapters 4.2 (Lead), 4.4 (Inorganic mercury), 4.5 (Carbon monoxide) and 7 (Preventive aspects). Lars Ole Goffeng, PsyD, PhD, STAMI, has written chapter 4.7 (Hydrogen sulphide). Chapter 1 (Introduction), 5 (Chemical substances' influence on cognitive domains) and summary were jointly written by Rita Bast-Pettersen and Gunilla Wastensson.

2. Methods

A systematic literature research was performed using PubMed with the assistance of Helen Sjöblom, librarian at the Biomedical Library, University of Gothenburg. The search string included various exposure terms, (for example aluminium and other exposures), outcome terms related to neuropsychological functions, and terms for different neuropsychological tests (as described in chapter 3), and was restricted to studies of occupationally exposed adults, written in English, Swedish, Norwegian or Danish. Only studies fulfilling a specific criteria set were included in the tables. We included studies with N>10 participants in which neuropsychological test methods were applied. To be included, the studies further had to include either a control or comparison group, or a differentiation of exposure, or comparison with established norms. In some studies demographic "facts" such as diagnosis of dementia were recorded under symptoms/diagnosis. In the studies where a diagnosis (for instance Alzheimer's disease) was the endpoint, only studies involving a neuropsychological test were included.

As previously mentioned, the study had to contain at least one test that could be classified as a neuropsychological test. The Mini Mental State Examination (MMSE) (Folstein et al. 1975) and the Clock Drawing Test (Shulman 2000) were accepted as neuropsychological tests. Neurological studies alone were not included, but some motor functions such as tremor or postural stability (sway), which are on the border between neuropsychology and neurology, were included. Unfortunately, no specific search term for tremor or sway was used. This would have been covered if we had included the term CATSYS (Danish Product Development 2000), but regrettably, no such term was included. The findings of tremor or sway may therefore be somewhat unsystematic, but they are often covered by the applied search terms.

The studies are presented in tables for each substance, or substance group in the result section, starting with the four metals (chapter 4). In the tables, the studies are presented in chronological order of publication. Experimental studies or patient studies were included in the tables where occupational studies were lacking, or as complements to such studies. Case studies with fewer than 10 subjects, as well as review studies on the topic, were mentioned in the text if deemed important.

We used a simplified scoring system. If one test result for a certain function was "positive" i.e., indicated impaired performance in the exposed group, this was categorized as a statistically significant difference denoted with a "+". The scoring system did not allow for more than one "+" for each function, and several tests indicating significant differences would not be scored higher than one "+". If none of the tests applied for that specific function were positive, the score was "-". In the same way, more

negative tests did not lead to more than one "-". Similarly, a near significant difference was denoted as "(+)". If the exposed group performed better than the control group, this was also denoted as "-". If there were no available tests for a specific function, no score was given.

By using this simplified system, the tables could not indicate the "strength" of the effects in the sense that the finding was supported by several tests. But since many epidemiological studies tend to apply few tests for each function, an increased number of "+" in one study could as well indicate that, "by accident", that study had applied more tests for that specific function than other studies with a stronger effect where only one test had been applied for the function.

The applied level of significance was set at $p < 0.05$. A difference between $p > 0.05$ and $p < 0.10$ was categorized as a near-significant difference.

References Methods

Danish Product Development (2000) CATSYS 2000 User's manual. Snekkersten, Denmark: Danish Product Development, Ltd.

Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12:189–198.

Shulman KI. Clock-drawing: is it the ideal cognitive screening test? Int J Geriatr Psychiatry 2000; 15:548–561.

3. Neuropsychological domains /functions

When dealing with individual subjects, evaluating how the person solves problems, works efficiently, or learns new strategies can be done through direct observations. Severe disturbances from neurotoxicants can also be observed clinically. This is not the case when the anticipated effects of lower exposure levels are smaller.

Neuropsychological tests are sensitive methods that are often used for detecting early functional impairments of the nervous system. Such test methods can also be used to systematically assess cognitive functions in large groups, providing measures that can be treated and analysed statistically.

There are several ways to classify neuropsychological domains. The present report can be read in connection with the report by Karlsson et al. (2014). Therefore, approximately the same classifications will be used in the present study, with four additional domains (the original Swedish definitions are given in parenthesis):

- General cognitive capacity and intelligence (generell kognitiv kapacitet och funktion) including verbal comprehension, verbal/academic skills (språkliga funktioner)
- Spatial skills/Perceptual organization (spatial kognition)
- Attention (uppmärksamhet)
- Memory and learning (minnesfunktioner), including: Attention/working memory, and

a. Auditory memory,
b. Visual memory
c. Spatial memory

- Executive functions (exekutiva funktioner)
- Speed (snabbhet) including processing speed (kognitiv snabbhet) and motor function/motor skills (motorisk snabbhet)

As motor functions are often affected by neurotoxicants, four domains not included in the report by Karlsson et al. were added in the present study:
Reaction time
Manual dexterity/manual speed
Tremor
Other motor functions/motor skills
Symptoms/diagnosis of mental impairment*

*Emotions and social cognition in the report by Karlsson et al. are classified as "Symptoms/diagnosis of mental impairment" in this study.

When testing workers in their workplace, the time allowed for data collection is usually limited, and most studies of occupationally exposed subjects use a limited number of tests. Therefore, in the literature on neurotoxic effects, descriptions of functions are not commonly used. A literary search must be based on test names, and not on the functions they are supposed to measure.

The WHO NCTB

Based on a 1983 meeting of an expert group, a screening battery of "core tests" for detecting neurotoxic effects in humans was composed. The goal was to sample the widest possible range of functions to detect any adverse change while completing testing within an hour. The test battery was named the World Health Organization Neurobehavioral Core Test Battery (WHO NCTB) (Anger 2014.) The battery included seven tests: Pursuit Aiming, Simple Reaction Time, Digit Symbol (WAIS), Santa Ana, Benton Visual Retention Test, Digit Span (WAIS), and Profile of Moods Scale (POMS) (Anger, 2014). Based on these recommendations a limited number of test batteries were composed, among them the Swedish Performance Evaluation System (SPES) (Iregren et al. 1996) and the Neurobehavioral Evaluation System (NES 2 & 3) (Letz 1990; Baker et al. 1985).

In order to study the possible effects of different exposures on neuropsychological functions, a description of the tests that are supposed to measure the underlying functions are necessary. In the following, the relevant functions are described in the same order as in the tables describing the outcomes of the exposures.

General cognitive capacity and intelligence

There are diverse conceptions of intelligence and how it can be measured. Among other factors, intelligence comprises the global capacity of a person to act purposefully, think rationally, and deal effectively with their environment (Lichtenberger and Kaufman 2013). It covers the ability to think, to reason and to understand, and to use previous experience to solve a new problem.

A central concept in the intelligence literature is the concept of general ability denoted by *g*. Lichtenberger and Kaufman (2013) describes *g* as a practical, clinical construct that corresponds to a person's full-scale IQ and which provides an overview of a person's diverse abilities. The *g* factor is not an ability in itself, but a construct derived from factor analysis.

One of the most used tests in neuropsychological test batteries is the Wechsler Adult Intelligence Scale (WAIS). The WAIS test is often

considered the gold standard for assessment of general cognitive capacity and intelligence (Strauss et al. 2006). In the same way, the WISC test is among the most used test for children. In the WAIS tests, the General Ability Index (GAI) is regarded as a better indicator of *g* than the full-scale IQ, and therefore regarded as better to assess the "pure" intelligence, especially in gifted persons. The GAI has a reduced emphasis on working memory and processing speed. In the WAIS test, GAI consists of a Verbal Comprehension Index and a Perceptual Reasoning Index (Flanagan and Harrison 2012).

Verbal comprehension (verbal/academic skills)

Verbal comprehension is a central element of a person's general intelligence. A certain degree of verbal comprehension is necessary for even minimal performance. It is a central factor/element of a person's general ability as denoted by *g*. When calculating IQ in the WAIS test, the "Verbal Comprehension Index" contributes 30 percent of the Full-Scale IQ.

Impairment of learned verbal skills such as reading, writing, and spelling can have profound effects on a subject's vocational competence and adjustment. It can also provide clues to the nature of the underlying condition (Lezak et al. 2012).

Neuropsychological tests regarded as covering verbal comprehension include:

In the WAIS-test:
WAIS Similarities
WAIS Vocabulary
WAIS Information
WAIS Comprehension

Other tests, not in the WAIS battery:
Aphasia Screening Test
Boston Naming Test

Verbal comprehension: a practical example.

A major reorganisation is planned at your workplace, which involves you having to perform some new work tasks. You receive new instructions, which are actually written in a somewhat complicated way. You manage to understand the new instructions ("Verbal comprehension/verbal intelligence") and you succeed in following the organisation plans.

Spatial skills/perceptual organization

Perceptual organization or perceptual reasoning is another central factor of a person's general intelligence. It covers nonverbal abstract problem solving, visual spatial reasoning, and the ability to quickly perceive visual details.

When calculating IQ in the WAIS test, the "Perceptual Reasoning Index" contributes 30 percent of the Full-Scale IQ.

Neuropsychological tests that are regarded as covering perceptual organisation or perceptual reasoning include:

In the WAIS-test tests for spatial skills:
WAIS Block Design,
WAIS Matrix Reasoning
Visual Puzzles
WAIS Picture Completion
Figure Weights

Other tests, not in the WAIS battery:
Tactual Performance Test-time
Raven Progressive matrices

Spatial skills/Perceptual organization: a practical example

You have bought a new kitchen from IKEA. You have brought with you all the elements, even the smallest parts. At home, you study the installation instructions/user manuals. ("Nonverbal abstract problem solving") Following the user manuals, you assemble the kitchen without encountering problems of any kind.

Processing speed/speed of information processing

Processing speed can be defined as the ability to perform simple, repetitive cognitive tasks quickly and fluently (Flanagan and Harrison 2012)–in other words, the time it takes a person to perform a mental task.

A central element in processing speed is "perceptual speed", the speed at which visual stimuli can be compared for similarity or difference. Another central element is the rate of test-taking; the speed and fluency with which simple cognitive tests are completed (Flanagan and Harrison 2012). In the WAIS test, the "Processing Speed Index" accounts for 20 percent of the Full-Scale IQ, but this index is not included when calculating the GAI.

Neuropsychological tests that are regarded as covering processing speed/ perceptual organisation or perceptual reasoning include:

In the WAIS-test:
WAIS Digit Symbol/Coding
WAIS Symbol Search
WAIS Cancellation

Other tests, not in the WAIS battery:
Trail Making Test A
Stroop Words
Stroop Color
Color Trails 1

Processing speed: a practical example

You have to check a manuscript that is about to be published. There are certain phrases that must be replaced throughout the manuscript, and you also need to check that the references are correct. ("The speed with which visual stimuli can be compared for similarity or difference"). The manuscript is printed on paper so you cannot use a proofreading program on PC. You're working to meet a very tight deadline. ("The time it takes a person to do a mental task").

Memory and learning including attention/working memory

Memory refers to the complex processes by which the individual encodes, stores, and retrieves information (Strauss et al. 2006). The memory systems can be categorized in different ways.
One categorization is between working memory and long-term memory.

Attention/working memory

The working memory, previously called short-term or immediate memory, refers to the ability to store information for a very short time, usually from a few seconds up to a couple of minutes. As this is not dependent on storing the information, it is usually classified as an element of attention. In the WAIS test, the "Working Memory Index" accounts for 20 percent of the Full-Scale IQ, but this index is not included when calculating the GAI.

Tests for attention/working memory:

In the WAIS-test:

WAIS Digit Span, forwards and backwards	(Auditory)
WAIS Arithmetic	(Auditory)
WAIS Letter-Number-Sequencing	(Visual)

Other tests, not in the WAIS battery:

Paced Auditory Serial Addition Test (PASAT)	(Auditory)
Seashore Rhythm Test	(Auditory)
Speech Sounds Perception Test	(Auditory)
Spatial working memory (CANTAB)	(Visual)

Attention/working memory: a practical example

You are asked to dial an eight-digit phone number, but you have nothing to write with, so you keep it in your head until you find the phone and switch it on. Then, you enter the eight-digit number and dial it correctly. ("Encode and retrieve information").

Long-term memory

Any information that needs to be retained for longer than a couple of minutes is stored in the long-term memory. The long-term memory is often divided into two major divisions: explicit (conscious or declarative) and implicit (unconscious or non-declarative or procedural).

Explicit memory covers intentional or conscious recollection of previous experiences. Explicit memory can be divided into two categories. On the one hand **episodic** memory, which stores specific personal (autobiographical) experiences, for instance recollections of a journey you made years ago. On the other hand, explicit memory also covers **semantic** memory, which stores factual information, independent of personal information, for instance the capital cities in a geographic region.

Implicit memory refers to a heterogeneous collection of abilities (priming, skill learning, or procedural memory). Examples of **skill learning** include how to swim, run a bicycle, put on your shoes, etc. There are indications that non-declarative memory is "phylogenetic"–older than declarative memory–and that this kind of memory is more robust in the face of damage to the nervous system (Hestad and Egeland, 2010). Most tests of long-term memory are tests of explicit memory, because this is the most realistic approach in a structured test setting.

Tests for "long-term" memory:

a. Verbal/auditory memory:
   Verbal paired associates (any version)
   Word-list learning (California Verbal Learning Test (CVLT), RAVL, WMS, 10, 12 or 15 words)
   Story memory/logical memory

b. Visual memory:
   Visual Paired associates
   Benton Visual Retention Test
   Rey-Osterreich complex figure
   Memory for faces (Warrington)

c. Spatial memory:
   TPT Location
   Spatial recognition memory
   Corsi Block Tapping Task

Long-term explicit memory: a practical example

You go to the store to buy groceries for the weekend. You do not bring a shopping list, because you expect to remember the things you need. You come home with 16 items, just what you needed and intended to buy. ("Explicit memory").

Long-term implicit memory: a practical example

You have been invited to take a winter holiday in the mountains. For various reasons, you haven't gone skiing for several years. It all works smoothly, you immediately remember how to ski, and the trip is a success. ("Implicit memory").

Executive functions

Executive function denotes a complex set of processes that have been broadly and variously defined (Strauss et al. 2006).

Lezak et al. (2012) describes executive functions as those capacities that enable a person "to engage successfully in independent, purposive, self-directed, and self-serving behaviour."

Although variously defined, most investigators believe executive processes are part of a system that acts in a supervisory capacity and encompasses skills necessary for purposeful, goal-directed behaviour. Problems with executive functions may manifest in a constellation of problems in everyday life. Examples are problems involving decision-making, following and adjusting plans, and distractibility. Central aspects are volition, planning, purposive action, and effective performance (Strauss et al. 2006).

Neuropsychological tests regarded as covering executive functions include:

Wisconsin Card Sorting Test
Trail Making Test B
Color Trails 2
Stroop test (color-words-interference)
Halstead Category Test
Letter Fluency FAS

Executive function: a practical example.

Suppose you have invited guests for dinner. ("Initiating/decision making"). You have planned what you want to serve and the time for the dinner. ("Planning/volition") You go to the shop and buy the food. ("Purposive action"). You clean the dining room/living room and set the table. You start preparing the food. ("Purposive action"). Suddenly, an old acquaintance who you haven't spoken to in a while calls and starts a conversation. ("Attentional shift"). You know that you have limited time, so you answer fairly briefly and agree to talk another day instead. ("Following and shifting plans, and the absence of distractibility") You finish your preparation, and at six o'clock, you're ready to welcome your guests.

Reaction time

Response speed can serve as a relatively direct way to assess processing speed. Simple reaction time is frequently slowed with brain disease or injury, and slowing increases with the complexity of the task. Complexity can be introduced through the addition of choices, requiring discrimination of stimuli, or the introduction of a distractor (Lezak et al. 2012). Reaction time differences between healthy and demented subjects become much larger when stimuli choices and/or response choices are introduced (Lezak et al. 2012).

Tests for reaction time:
NES 2&3
SPES
Cambridge Neuropsychological Test Automated Battery (CANTAB)

Simple reaction time: a practical example

You're driving a car when suddenly, a child runs out into the road. You brake immediately and manage to prevent an accident. ("Simple reaction time").

Choice reaction time: a practical example

You're driving a car in Paris, and drive into the roundabout at Etoile which has 12 access roads. Traffic is moving fast and you succeed at switching lanes several times and getting yourself through the roundabout. ("Choice reaction time").

Manual dexterity/manual speed

Tests of manual agility have frequently been included in neuropsychological examinations. Brain disorders often, but not always, tend to have a slowing effect on finger tapping rate. There is evidence that pegboard-placing speed is reduced by a number of conditions including toxic exposure (Strauss et al. 2006).

Tests for manual dexterity/manual speed:
Grooved Pegboard Test
Purdue Pegboard Test
Finger Tapping Test/Finger Oscillation Test

Manual dexterity/manual speed: a practical example

You keep a mess of screws and nails in your workshop drawer. You've decided to clean it up and throw out whatever you don't need, and give the small screws to a neighbor who has an urgent need for screws. You get this drawer sorted in no time, ("Manual speed") even though many of the screws are very small ("Manual dexterity").

Tremor

Tremor is defined as "any involuntary, approximately rhythmic, and roughly sinusoidal movement of a body part". It is produced by alternating or synchronous contractions of antagonist muscles. It is characterized by its frequency, which is the number of cycles per second (Hz), and by its amplitude. A slight, barely visible physiologic tremor appears normally in all humans and may be enhanced in the presence of factors such as fatigue, anxiety, or certain medical conditions. Nicotine exposure also increases the amplitude of physiologic tremor. Exposure to several neurotoxins has been reported to cause tremor (Wastensson et al. 2016).

Tests for tremor:
CATSYS TREMOR
Nine-hole Steadiness/Static Steadiness Test
Motor Steadiness test

Tremor: a practical example

You are a guest at a party where you have to pick up a cup of coffee from the other end of the room. The coffee is served in small, delicate porcelain cups. Fortunately, your hands are not trembling, unlike the man sitting at the same table as you. ("Tremor/steadiness"). He has a hand tremor, and you can hear his cup clinking whenever he moves.

Other motor skills

Grip strength measures are included in neuropsychological examinations in order to assess gross and subtle motor impairment. Grip strength declines with age. There is evidence that changes in grip strength correlate moderately with changes in cognitive functioning. The decline appears to be caused by a common factor or factors that are responsible for age-related deterioration in cognitive and non-cognitive processes (Strauss et al. 2006).

Tests for other motor skills:
Hand Dynamometer/Grip Strength
Eurythmokinesimeter (EKM)
Pursuit Aiming

Other motor skills: a practical example

You just bought a jar of jam that you are about to open. But the lid is stuck very tight, and you have trouble getting a proper grip. Fortunately, your hands are strong, and you manage to unscrew the lid. ("Grip strength").

Symptoms/diagnosis of mental impairment

Subjective complaints can be an early indication of encephalopathy. A greater number of symptoms has been associated with cumulative exposure to solvents, and has been observed among patients with the diagnosis psychoorganic syndrome. Symptom questionnaires are commonly used to monitor workers who are occupationally or environmentally exposed to neurotoxicants, shift work, bullying, and the like (Bast-Pettersen 2006).

Symptom questionnaire used in occupational health settings:
Profile of Mood Scale (POMS)
Q16 (Bast-Pettersen 2006)
Euroquest
In the present study, we also include the finding of a diagnosis of, say, dementia, if this is in a study that has applied a neuropsychological test.

Symptoms: a practical example

You often find it difficult to concentrate. ("Symptom of mental impairment").

The diagnostic accuracy of neuropsychological tests

When using neuropsychological tests, we need to know the proportions of patients with normal or "abnormal" neuropsychological function that is likewise to be "diagnosed" by the test(s). The terms "positive" and "negative" refer to the presence or absence of the condition of interest (Altman, 1995), which is impaired/reduced nervous system function in our study.

The **sensitivity** of a test is the proportion of "positive" or "sick" persons that are correctly identified by the test.

The **specificity** is the proportion of negatives, i.e., the healthy subjects that are correctly identified by the test.

There is no single neuropsychological test that can give a precise result in isolation. Neuropsychologists use a test battery composed of a varying number of tests to assess cognitive function.

In a study by Heaton and colleagues, the test results of 329 patients who already had verified structural brain pathologies (cerebral disorders) were examined using a neuropsychological test battery. All in all, the sensitivity (correct classification of brain damaged subjects) and specificity (correct classification of normals) were both 83 percent (Heaton et al. 1991).

In studies of subjects with more diffuse/unclear conditions than verified structural brain pathology, the sensitivity and specificity is expected to be lower (Bast-Pettersen, 2008). Österberg et al. (2000), in a study of subjects with chronic toxic encephalopathy, found the sensitivity to be 77 percent and the specificity to be 72 percent when comparing subjects with chronic toxic encephalopathy with healthy referents.

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4. Results

4.1 Aluminium

Aluminium (Al) is the third most common element in nature after oxygen and silicon. It is the most abundant metallic element, representing about eight percent of the earth's crust by weight. It is a light metal, with a specific gravity of 2.7. It does not occur in metallic form in nature, but its compounds are present in almost all rocks, soils, and clays. Bauxite is the main aluminium ore.

The metal is used in aircraft, train, and car construction, as well as in building materials, electrical conductors, kitchen utensils, and packaging. Aluminium is not known to serve any essential biological function in the human body. To the extent that aluminium is accumulated in the body, this occurs mainly in bone (50%), lungs (25%), kidney and liver. The brain has a lower aluminium concentration than many other tissues, and the primary site of aluminium entry to the brain is through the blood-brain barrier (Sjögren et al. 2015). It has been suggested that aluminium binds to transferrin and crosses the blood-brain barrier via the iron-transport system (Edwardson and Candy 1989).

For persons not occupationally exposed, the most important sources of intake are food, including baking powder, bakery products and mixes for bakery wares, dried vegetables, infant formulas, food additives, and drinking water. The aluminium content of food is generally lower in fresh meat and fish, and higher in vegetables, grains, and spices (Sjögren et al. 2015). The bioavailability of aluminium from food can be affected by the presence of food in the stomach. The presence of food generally reduces/inhibits aluminium absorption, but the presence of citrate, for example from orange juice, enhances aluminium absorption (Yokel and McNamara 2001). The daily median aluminium intake is less than 10 mg, and urine excretion accounts for more than 95% of aluminium excretion (Sjögren et al. 2015).

Other sources are medicinal products containing aluminium (especially antacids), vaccines, and cosmetic products (especially antiperspirants) (Bast-Pettersen 2000; Bast-Pettersen et al. 2000). There is no evidence to suggest that the use of deodorants significantly contributes to daily aluminium absorption (Yokel and McNamara 2001).

Scientists have searched for a possible connection between the presence of aluminium in the central nervous system and the occurrence of nervous system diseases. Aluminium has been proposed as a causative agent in development of neurodegenerative diseases, and/or as a disease marker.

The aluminium and Alzheimer's disease hypothesis:

Alzheimer's disease (AD) is a neurodegenerative disease that causes brain cell death. This progressive disease causes a distinct pattern of pathological changes in the brain.

Neurofibrillary tangles (NFT) are abnormal accumulations of a protein called tau that collect inside neurons. Brain nerve cells (neurons) have a special transport system (microtubules) that transports nutrients, molecules, and information to other cells. The important, fiber-like tau protein is responsible for keeping the microtubules stable. In Alzheimer's disease, the threads of tau begin to pair with other threads, becoming tangled and twisted, and thus creating neurofibrillary tangles (NFT). Due to this malformation, the microtubules become unstable and disintegrate, which collapses the entire neuron transport system.

The **beta-amyloid** protein involved in Alzheimer's appears in several different molecular forms that collect outside and around the brain's nerve cells. It is formed from the breakdown of a larger protein, called amyloid precursor protein (APP). Patients with Alzheimer's disease have a buildup of these plaques.

One of the sites in the brain that are usually affected in an early stage is the hippocampus, which is central to memory function. The hippocampus is also essential to spatial memory and spatial navigation, and it is suggested that early hippocampus damage may explain why people with AD often wander and get lost.

In 1965, Wisniewski, Terry and Klatzo published studies that showed that introducing aluminium salts into the brain of rabbits induced cognitive deficits and the formation of neurofibrillary changes that, with conventional silver staining, seemed similar to the neurofibrillary tangles present in the brain of AD sufferers (Lidsky 2014).

In 1976, the dialysis encephalopathy syndrome was described. A group of dialysis patients suffered serious neurological disturbances (Alfrey et al. 1976). The dialysis fluid contained aluminium, meaning that these patients who were suffering from kidney disease were both heavily exposed to aluminium and practically unable to excrete it.

It was later discovered that, contrary to the initial findings by the research group led by Wisniewski, Terry and Klatzo, aluminium salts did not prove to induce neurofibrillary changes similar to the neurofibrillary tangles of Alzheimer's disease (Bast-Pettersen et al. 1994; Lidsky, 2014).

Further, the hypothesized similarity between aluminium-induced dialysis encephalopathy and Alzheimer's disease was shown to be incorrect. Dialysis encephalopathy turned out to be caused by aluminium, but it resulted in a different neuropathology.

The above findings led to the study of several neurodegenerative diseases, but most of the research concentrated on Alzheimer's disease, with a focus on whether aluminium might cause or contribute to the disease. It has also been discussed whether elevated aluminium concentrations in Alzheimer's sufferers could be a consequence of disease, for example, if already existing disturbances in the blood-brain barrier may allow more aluminium to cross it, or if neurofibrillary tangles and beta-amyloid plaques may bind aluminium (Yokel 2000).

Aluminium in drinking water

Most epidemiological studies on aluminium and dementia have focused on aluminium in drinking water as the source of exposure. The main sources for aluminium in drinking water are on the one hand dissolved aluminium as a result of leaking from minerals in the soil and bedrock, and on the other hand the aluminium used in water treatment to reduce the number of small particulates. Aluminium in drinking water accounts for only a fraction of the amount taken in via food and drink, probably around 1% (Yokel 2000) or up to 2.2% (Willhite et al. 2014).

Sjögren and colleagues summarized the research relating to drinking water: "The results of several epidemiological studies suggest a small increased risk of dementing illnesses, including Alzheimer's disease, for people living in areas of higher compared to lower water aluminium concentrations. However, there are also several reports of no associations. The inconsistent findings from autopsy and from epidemiological studies of water aluminium contribute to the controversy surrounding the role of aluminium in the etiology of Alzheimer's disease. Even if aluminium is elevated in the brain from Alzheimer's patients, it does not prove a cause-effect relationship because Alzheimer's disease may produce changes in cells or cell debris that more effectively bind aluminium" (Sjögren et al. 2015).

Occupational exposure to aluminium

Unlike the modes of exposure that are associated with dialysis treatment or drinking water, occupational exposure to aluminium is by inhalation (Bast-Pettersen et al. 1994). Aluminium made available via the lungs, as in occupational settings, is probably absorbed to a greater extent than aluminium entering the body via the gastrointestinal tract (Yokel and McNamara 2001; Willhite et al. 2014). Studies have showed elevated concentrations of aluminium in serum and urine among aluminium-exposed workers (Sjögren et al. 1985), which confirms that aluminium has been absorbed.

The first epidemiological studies on aluminium-exposed workers applying neuropsychological tests were published in the early 1990ies (Rifat et al. 1990; Hosovski et al. 1990; Bast-Pettersen et al. 1994; Hänninen et al. 1994). The first study was on underground miners who had inhaled aluminium

dust ("McIntyre Powder") to protect themselves from the pulmonary disease silicosis (Rifat et al. 1990). They were examined with three tests (MMSE, SDMT and Raven). The 261 workers performed less well than the 346 referents. Biological measures were not available, the only exposure parameter was the number of years worked. However, according to Cherry (1992), the referents had longer education, and the exposed subjects with the longest duration of exposure had the shortest education. Further, a larger proportion of the referents had English as their mother tongue. On reanalysing the data, a larger estimated effect was found among miners who had another mother tongue than English (Rifat 1992).

A study from former Yugoslavia found slower psychomotor reaction, reduced memory, and "disturbance of the mental balance" in workers in an aluminium foundry (Hosovski et al. 1990).

In a study of elderly workers employed in a primary aluminium plant, those who worked in the potroom with Søderberg electrolytic cells performed less well on a test for tremor. Further, there was a tendency towards a greater number of self-reported symptoms and lower performance in tests for psychomotor tempo and visuospatial organization (Bast-Pettersen et al. 1994).

In a later study of aluminium welders, the welders performed better than the referents on a tremor test (Bast-Pettersen et al. 2000). However, among the welders, years of exposure, but not age, was predictive of poorer performance on the tremor test. There was also an association between slower reaction time and aluminium in the air, and the exposed welders reported slightly more symptoms (Bast-Pettersen et al. 2000).

In the following years, the only studies that applied a tremor test were the study by Sim et al. (1997) and the studies conducted by the German research team headed by Kiesswetter and Buchta. These studies did not find an increased prevalence of tremor among workers exposed to aluminium.

A meta-analysis reported evidence of neuropsychological effects in workers exposed to aluminium (Meyer-Baron et al. 2007). The meta-analysis included nine studies comprising 449 exposed subjects and 315 referents. They analysed six tests yielding ten performance variables. Several of the test results indicated an inferior performance for the exposed group, but the only significant overall effect obtained was for a test of speed of information processing, the Digit Symbol test. As the meta-analysis included tests that were applied in at least three studies, the only test of motor function that was included was a test for manual dexterity/manual speed, the Santa Ana test.

The German Commission for the Investigation of Health hazards of Chemical Compounds in the work area has suggested a no observed adverse level of 50 µg Al/g creatinine in urine for subtle neurotoxic effects (Klotz et al. 2018). The question whether occupational exposure to aluminium can impact the nervous system remains unsettled.

Occupational exposure limit values (Sweden): 5 mg/m^3 (total dust) and 2 mg/m^3 (respirable dust) Arbetsmiljöverkets författningssamling (AFS) 2018:1.

Conclusions

Altogether, 559 papers were identified in the literature search. Among these, 24 studies were found to fulfil our inclusion criteria and subsequently included in the table.

When summing up the results, there are no clear, consistent findings. In line with the aluminium Alzheimer's hypothesis, several studies included tests for attention or working memory, but yielded as many positive as negative findings. Four studies included tests for verbal or visual memory, but among these the White et al. (1992) study had several methodological weaknesses, including self-selection of symptomatic workers.

There was a slight tendency towards positive findings related to speed of information processing, which is in line with the meta-analysis by Meyer-Baron et al. (2007). The finding that few studies reported no effects on verbal/academic skills could be explained by the fact that the groups were often matched according to verbal/academic skills.

Neither reaction times nor motor tests were found to be associated with aluminium exposure in the majority of the studies. The finding of more symptoms among the exposed groups could be an indication of a possible, slight effect from exposure, but it might also be related to the fact that the subjects underwent thorough examination, which may have made them more alert to possible symptoms that they might otherwise have been.

Table1. Neuropsychological effects in workers exposed to aluminium.

Epidemiological studies of exposed workers	N Expo/ referents	Type of exposure characterization	Years exposed	Verbal/ academic skills	Spatial skills/ perceptual organization	Speed information processing	Attention/ working memory	Verbal memory	Visual memory	Executive functions	Reaction time	Manual dexterity/ speed	Tremor	Other motor skills	Symptoms/ diagnosis
Rifat SL, et al. Lancet. 1990	261 /346	Y;	>20/10-20 <10		+	+									
Hosovski E, et al. Med Lav. 1990	87/ 60	Y; A; B; U;	18.9	-	+	+	+				+				
White DM et al. Arch Intern Med. 1992[a]	25/-	Y;	18.7	-	-			+	+						+
Bast-Pettersen R et al. Am J Ind Med. 1994	14/8/ 16	Y: A; S; U;	19.2/ 19.6	-	(+)	-	-			(+)	-		+		+
Hänninen H et al. Scand J Work Environ Health. 1994	17/-	Y; S; U;	15						+		+				-
Sjögren B et al. Occup Environ Med. 1996	38/39	Y; B; U;	17.1	-			-				-	+		+	+
Sim M et al. Occup Environ Med. 1997[b]	63/37	A;	> 10	-							-		-	-	+
Kilburn KH.. 1998[a c]	41/ 32-36		NA			+				+	+			+	+
Akila R et al. Occup Environ Med. 1999[a]	24/27/28	S; U;	NA		(+)	+	-			-	-	-			
Bast-Pettersen R et al. Am J Ind Med. 2000	20/20	Y; A; U;	8.1								+		+		+
Riihimäki V, et al. Scand J Work Environ Health. 2000[a]	30/29/ 25	S; U;	NA												+
Letzel S, et al. Neurology. 2000	32/30	Y; P; U;	13.7	-	-	-	-				-				
Iregren A. et al. Occup Environ Med 2001[f]	119-16-38/ 39	Y; B; U;	15/ 8/ 15	-		-					+	+		-	+
Polizzi S et al. Neurotoxicology. 2002	64/32	Y; S;	25.4		+		+								

Differences between groups in neuropsychological performance/or differences related to exposure parameters: Large/ Statistically significant different (Red) Tendency/Near significant (blue) No difference (green). p <0.05+; p 0.05 -0.10 (+); p >0.10 -;

Type of exposure characterization: Air: A; Blood including whole blood (B), Serum (S) or Plasma (P); Urine: U. Duration of exposure (presented as hours in some studies), but calculated as years of exposure.

(continuation) **Table1. Neuropsychological effects in workers exposed to aluminium.**

Epidemiological studies of exposed workers	N Expo/ referents	Type of exposure characterization	Years exposed	Verbal/ academic skills	Spatial skills/ perceptual organization	Speed information processing	Attention/ working memory	Verbal memory	Visual memory	Executive functions	Reaction time	Manual dexterity/ speed	Tremor	Other motor skills	Symptoms/ diagnosis
He SC et al. Int J Immunopathol Pharmacol. 2003	32/34	Y; A; U;	14.9			+					-				+
Buchta M. et al. Int Arch Occup Environ Health. 2003	98/50	Y; A; P; U;	6	-	-	-	-				+	-			-
Buchta A M et al. Environ Toxicol Pharmacol. 2005	44/37	Y; A; P; U;	11.4	-	+	+	+				(+)	-	-		-
Kiesswetter E. et al. Int Arch Occup Environ Health. 2007[g]	20/12	Y; A; P; U;	15	-	-	(+)	-				-	-	-		-
Kiesswetter E. et al. Int Arch Occup Environ Health. 2009[g]	92/50	Y; A; P; U;	8.8	-	-	-	-				-	-	-		-
Deschamps FJ. Et al. J Occup Environ Med. 2009	30/60	Y; A; P; U;	6.5	-	-		-								-
Giorgianni CM. et al. Toxicol Ind Health. 2014[h]	86/-	Y; A; B	16?			+	+	+	+						
Lu X. et al. J Occup Environ Med. 2014[i]	66/70	Y; S;	30.2	+			+								+
Zawilla NH. et al. J Inorg Biochem. 2014	54/51	Y; A; S,	21.6	-	+		+	+		+					
Yang X. et al. J Occup Environ Med. 2015[h]	91/184 /91	Y; S;	21.2	+			+								+
Number of studies with + / -				2+; 13-	5+; 2(+); 6-	7+; 1(+); 5-	7+; 8-	3+	3+	2+; 1(+); 1-	6+; 8-	2+; 5-	2+; 5-	2+; 2-	11+; 6-

Differences between groups in neuropsychological performance/or differences related to exposure parameters: Large/ Statistically significant different (Red) Tendency/Near significant (blue) No difference (green). p <0.05+; p 0.05 -0.10 (+); p >0.10 -;

Type of exposure characterization: Air: A; Blood including whole blood (B), Serum (S) or Plasma (P); Urine: U. Duration of exposure (presented as hours in some studies), but calculated as years of exposure.

Notes

a. The subjects were recruited by self-selection. The subjects were symptomatic workers.

b. Some of the results are also published in: Dick RB et al. Neurotoxicol Teratol. 1997. The Dick RB et al. study focuses on tremor, and no tremor was observed. As the Dick et al. study can be regarded as a double publication, it is not included in the table.

c. In addition to being self-selected, health-concerned subjects, the exposed workers were 6 years older than control group "a" and 3 years older than in control group "b". No measures of exposure were provided.

d. Akila R et al. Occup Environ Med. 1999; and

e. Riihimäki V, et al. Scand J Work Environ Health. 2000 published results from the same subjects in a slightly different wayThe Symptom score is from the Riihimäki V, et al. study.

f. Part of the sample, 38 welders and 39 referents, was presented in Sjögren et al, 1996.

g. The subjects seem to have been split into two different cohorts based on different companies (automobile vs trains and trucks).

- Kiesswetter E. et al. Int Arch Occup Environ Health. 2007, is a follow-up of the study by Buchta A M et al. Environ Toxicol Pharmacol. 2005.
- Kiesswetter E. et al. Int Arch Occup Environ Health. 2009 is a follow-up of Buchta M. et al. Int Arch Occup Environ Health. 2003.

h. This study exhibits several methodological weaknesses. The presentation of the results in this study is very unclear, and it is thus difficult to evaluate their findings.

i. The only test applied was the Mini Mental State Examination (MMSE).

References Aluminium

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4.2 Lead

Lead (Pb) is a metallic element that generally occurs as an environmental pollutant (in air, soil, water and food). It has long been used in a variety of products such as coins, colour pigments, and pans, as well as in alloys, soldering, and drinking water pipes. Contemporary uses for lead are in car batteries, colour pigments, ammunition, and in solder points used in various electronics products. Lead can also be included in certain alloys when manufacturing parts for products where the shape is a priority, such as keys and water taps.

The general population is mainly exposed to lead through food, although foods nowadays generally contain low levels of lead. The lead content in drinking water is normally low, but elevated lead levels in individual wells have been demonstrated in some areas in Stockholm, Skåne, and Dalarna (Harari et al. 2017). Other sources of exposure are meat from game shot with lead bullet or lead shot, lead-glazed ceramics, and certain health food preparations, as well as brass components used in drinking water systems, water taps, and in coffee machines. Lead in soil and dust can be a source of exposure for toddlers who are eager to put objects in their mouths (Skerfving and Bergdahl, 2015).

Previously, lead was used as an additive in gasoline, which resulted in significant exposure through inhalation of car exhaust fumes. Since the use of lead as an additive in motor gasoline was discontinued in 1995, the Swedish population's lead exposure has decreased significantly. Although the levels have decreased significantly over time, the average lead blood level in children (9 µg/L) is still such that there is very little margin to the low-risk level for effects on the development of the brain and nervous system (IMM 2017). The average blood levels of lead are 5–30 µg/L in adults without occupational exposure (Sällsten and Barregård 2014).

Lead is absorbed to about 50 percent when inhaled, while absorption through the gastrointestinal tract is about 15–20 percent. After absorption, lead is found in the red blood cells in the blood and is transported to most organs in the body. Lead is excreted via urine and faeces, and the half-life for lead in blood and most other organs in the body is around 1½ months. Lead accumulated in the skeleton has a longer half-life (5–20 years), which means that after prolonged exposure (years), when a pool of lead is built up in the skeleton, lead in the blood will decrease more slowly. Lead concentration in blood (B-Pb) is the most commonly used biomarker of exposure, but the concentration in bone is often used in epidemiological studies as it reflects long-term exposure better than B-Pb (Skerfving and Bergdahl, 2015).

The toxic effects of high exposure to lead have been known for a very long time. In acute poisoning, headache, irritability, and severe colic-like stomach pains can be seen (lead colic). In mild cases insomnia, restlessness and coordination difficulties may occur, and in severe cases, acute psychosis, confusion, loss of consciousness, and epileptic seizures. In lower doses, effects on the central and peripheral nervous system, inhibited blood formation, and impacted kidney function are seen (EFSA 2010). In cases of moderate exposure, effects on heart vessels, including increased risk of high blood pressure, have been reported (Gambelunghe et al. 2016). For prolonged, low exposure, a more non-specific clinical picture involving fatigue and poor appetite is seen.

Lead passes over to the foetus during pregnancy via the placenta and is also passed on through breast milk. The lead content of the new-born child is associated with the level of the mother, but slightly lower. If the woman has had a blood lead content of 0.8 µmol/L during pregnancy, this clearly exceeds the blood levels at which harmful effects have been shown in children. Growing foetuses and young children are highly sensitive to lead, and early life exposure has been linked to inhibited development, impaired intellectual capacity (lower IQ), and behavioural disorders (EFSA 2010). At the group level, subtle but measurable effects on motor skills and cognition have been shown at lead levels <0.24 µmol/L. An increased risk of behavioural disturbances during childhood and adolescence has also been seen at these levels in some studies. Impact on IQ has been observed at levels as low as 0.14 µmol/L, and no threshold value has yet been detected by means of dose-response analyses (Lanphear et al. 2005).

Some studies suggest that lead exposure may result in reduced fertility, an increased risk of miscarriage, and reduced birth weight. Some of these effects, such as the effect on sperm and reduced fertility, have been observed at blood levels around 1.5–2.0 µmol/L (Skerfving 2005).

Occupational exposure

Occupational exposure may occur in lead smelters, brass and bronze foundries, glassworks, battery manufacturing plants, and facilities where objects painted with red lead are processed. Welding or cutting of materials painted in lead may result in high exposure levels. Welders processing materials containing lead without using respiratory protection or extractors have been reported as having more than the double level of lead in their blood (Dössing and Paulev 1983). In a previous study, workers performing various recycling tasks were shown to have elevated exposure to toxic metals, including lead (Julander et al. 2014).

Occupational exposure occurs mainly through inhalation, but lead can also be absorbed through the gastrointestinal tract through contamination of food, snuff, and cigarettes. Large variations in blood lead levels may occur at the same air lead level due to individual factors such as previous lead exposure, various large background exposures, and differences in lead metabolism. The impact of working conditions and working methods on hand-mouth transport of lead is also of great importance. Impairment of performance in neurobehavioral tests appears at blood levels of 40 µg Pb/100 mL and above (SCOEL 2002).

Occupational exposure and biological limit values

The occupational exposure **limit value** is 0.1 mg/m^3 for inhalable dust and 0.05 mg/m^3 for respirable dust (Arbetsmiljöverkets författningssamling (AFS): 2018:1). Those with occupational exposure to lead are covered by a monitoring system that involves periodic medical examinations and **biological exposure control** of the lead content in their blood, along with rules dictating that they must discontinue work if they acquire high levels of lead in their blood. The blood limit values are 0,5 µmol/L (10 µg Pb/100 mL) for women<50 years, and 1,5 µmol/L (30 µg Pb/100 mL) for women>50 years and men, respectively (Arbetsmiljöverkets författningssamling AFS): 2019:3). Pregnant or nursing women may not be employed in work with lead (Arbetsmiljöverkets författningssamling (AFS): 2007:5).

Neuropsychological effects in workers exposed to lead

In the present literature search, 805 papers in all were listed in the initial search. We did not include studies of residents living in communities with environmental exposure or exposure to lead in the prenatal period or childhood. 24 papers were review papers or could serve as background information for health effects due to lead-exposure. 53 studies were selected for a further evaluation. Studies on workers exposed to organic lead (i.e., organolead manufacturing workers) were not included. **37** papers fulfilled the inclusion criteria and were included in the final literature review. All studies covered neuropsychological effects associated with occupational exposure to inorganic lead. Most papers were cross-sectional studies, but one study reported results from testing before and after exposure began (Mantere et al. 1982). Workers and controls performed similarly at the first examination, but exposed workers' performance was inferior to controls at follow-up two years later, particularly in the Block Design test, Santa Ana coordination and Digit span test.

Khalil et al. (2009) reported an association between cumulative exposure to lead and decrease in cognitive performance as assessed with tests of spatial skills, learning and memory, and general intelligence, especially among workers >55 years.

When summing up the results in the table, 15 out of 20 studies found decrements in manual dexterity and speed. The tests used in these studies were the Santa Ana dexterity test (Hänninen et al 1978; 1998; Mantere et al. 1982; Baker et al. 1985; Chia et al. 1997) finger tapping test (Grandjean et al. 1978; Pasternak et al. 1989; Matsumoto et al. 1993; Chuang et al. 2005; Chen et al. 2005; Fenga et al. 2016), Groved Pegboard (Ryan et al. 1987; Chia et al. 1997) and Purdue pegboard (Lindgren et al. 1996; Hwang et al. 2002; Schwartz et al. 2005). More positive than negative findings were also seen for spatial skills, memory, and executive functions along with subjective symptoms. In most studies, all participants were male, but both sexes were included in some studies. However, outcome results were not reported separately for men and women.

Meyer-Baron and Seeber (2000) performed a meta-analysis of 22 studies covering occupational exposure conditions of <70 µg/100 ml blood lead. 13 tests from 12 studies were included in the analysis, and deficits were found for the tests Block Design, Logical Memory, and Santa Ana; these were interpreted as 'small' effects. The extent of the exposure related to the decrease of performance was comparable to those changes of performance that can be expected during up to 20 years of aging.

In a subsequent study, the authors summarized two different meta-analytical reviews of 24 selected publications (Seeber et al. 2002). Two out of six tests of learning and memory showed impairments, covering Logical Memory and Visual Reproduction. Four out of seven tests of attention and visuospatial information processing showed impairments (Simple Reaction, Attention Test d2, Block Design Picture Completion), as did three out of four tests for manual dexterity and other motor skills (Santa Ana, Grooved Pegboard, and Eye-hand Coordination).

Goodman et al. (2002) performed a systematic review and meta-analysis of 22 studies covering occupational exposure conditions of <70 µg Pb/100 ml blood lead. Data were extracted for only those tests that were included in at least three studies, and 22 tests met the inclusion criteria. Two tests (digit symbol and d-2 errors) showed significant effects in all three models used (fixed, weighted random and unweighted random).

In a recent review (Mason et al. 2014), the authors pointed out the adverse effects of lead exposure on visuospatial ability, along with associated declines in intelligence, memory, processing speed, comprehension and reading, and motor skills.

Conclusions

Our findings indicating decrements in manual dexterity and speed following exposure to lead are in line with the findings by Meyer-Baron and Seeber (2000), Seeber et al. (2002) and Mason et al. (2014). Adverse effects on spatial skills was reported in all four review papers whereas memory deficits were reported by Meyer-Baron and Seeber (2000), Seeber et al. (2002), and Mason et al. (2014). Decrements in cognitive functions may remain after cessation of exposure and may also cause progressive cognitive decline with age (Khalil et al. 2009; Mason et al. 2014).

Table 2. Neuropsychological effects in workers exposed to lead.

Epidemiological studies of exposed workers	N Expo/ Referents	Type of exposure characterization	Years exposed	Verbal/ academic skills	Spatial skills/ perceptual organization	Speed information processing	Attention/ working memory	Verbal memory	Visual memory	Executive functions	Reaction time	Manual dexterity/ speed	Tremor	Other motor skills	Symptoms/ Diagnosis
Haenninen H, et al. J Occup Med 1978[a]	49/24	B;	2–9	-	+	+	+	-	+			+			+
Grandjean P, et al. Scand J Work Environ Health 1978	42/22	B; H;	2	+	+	+	+	+	+			+			
Mantere P, et al. Neurobehav Toxicol Teratol. 1982[b]	I :24/33 II: 16/31	B;	2		+	-	+	-				+			
Baker EL, et al. Acta Psychiatr Scand Suppl. 1983[c]	103/61	B;	0.65	+		+		+	+						+
Hogstedt C, et al. Br J Ind Med. 1983	49/27	B;	18	-		-		+	+	-	+	-			+
Baker EL, et al. Br J Ind Med. 1984[d]	99/61	B;	23.4	+			(+)	+							+
Baker EL, et al. Br J Ind Med. 1985[e]	160/65; 43/34; 38/19	B;	-	(+)	(+)	-	-	+				+			+
Williamsson AM, et al. Br J Ind Med. 1986	59/59	B;			+	+	-	-	-				+		
Ryan CM, et al. Int J Neurosci. 1987[f]	288/181	B;		-	-		-	-	-			+			
Boey KW, et al. Toxicology. 1988[f]	49/36	NA		-	-	+	-	-			+	-			
Banks HA, et al. Sci Total Environ. 1988[g]	13/18/-	B;		+											
Pasternak G, et al. J Toxicol Clin Toxicol. 1989	24/29	B; A;	2.8	-		-	+					+		+	+

Differences between groups in neuropsychological performance/or differences related to exposure parameters: Large/ Statistically significant different (Red) Tendency/Near significant (blue) No difference (green). p <0.05+; p 0.05 -0.10 (+); p >0.10 -;

Type of exposure characterization: Blood (whole blood): B; BO: bone; H: hair; Y: year. Duration of exposure (presented as hours in some studies), but calculated as mean years of exposure.

(continuation) **Table 2. Neuropsychological effects in workers exposed to lead.**

Epidemiological studies of exposed workers	N Expo/ referents	Type of exposure characterization	Years exposed	Verbal/ academic skills	Spatial skills/ perceptual organization	Speed information processing	Attention/ working memory	Verbal memory	Visual memory	Executive functions	Reaction time	Manual dexterity/ speed	Tremor	Other motor skills	Symptoms/ diagnosis
Stollery BT, et al. Br J Ind Med. 1991	22/22 /26/-	B;		-		+	+	+	-		+				
Matsumoto T, et al. Environ Res. 1993[h]	27–48/-	B;										+			
Maizlish NA, et al. Occup Environ Med. 1995	43+45/-	B;	4			-	-		-		-	-			+
Stollery BT, et al. Neurotoxicol Teratol. 1996	70 (22+22 +26)/-	B;	NA								+				
Lindgren KN, et al. Occup Environ Med. 1996	467/-	Y; B;	17.7		-	+	-	+		+		+			
Chia SE, et al. Neurotoxicology 1997	50/97	B;	-				+		-			+			-
Osterberg K, et al. Sci Total Environ. 1997	38 (19+19)/-	B; BO;	10		-		-	-	-						-
Hänninen H, et al. Occup Environ Med. 1998 [i]	54 (28+26)/-	B;			+	+	+	+			-	+			(+)
Lucchini R, et al. Neurotoxicology. 2000	66/86	B; Y;												+	+
Hwang KY et al. Environ Health Perspect. 2002	212/-	B;	8.8	-		-	-	-	-	+	+	+			
Kumar P, et al. Vet Hum Toxicol. 2002	60/30	B; Y;			+		+		+						
Barth A, et al. Int Arch Occup Environ Health. 2002	47/53	B;	11.7		+	-	+			+	-				
Fiedler N, et al. Am J Ind Med. 2003	40/33	BO;				+	-	-	-	-	+	-			-
Lindgren KN, et al. Arch Environ Health. 2003[j]	40+40/-	B;			-	-		+		-		-			

Differences between groups in neuropsychological performance/or differences related to exposure parameters: Large/ Statistically significant different (Red) Tendency/Near significant (blue) No difference (green). p <0.05+; p 0.05 -0.10 (+); p >0.10 -;

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(continuation) **Table 2. Neuropsychological effects in workers exposed to lead.**

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Schwartz BS, et al. Epidemiology 2005[k]	576/-	B; BO;				-	-			+	-	+		+	-
Bleecker ML, et al. Occup Environ Med. 2005	256/-	B; Y;	17.1					+							
Chuang HY, et al. Neurotoxicol Teratol. 2005	27/-	B;		-		+	-	-	+			+			-
Winker R, et al. Int Arch Occup Environ Health 2006[l]	47+48/-	B;			+	-			-	+	-				
Chen SS, et al. J Occup Environ Med. 2005[m]	33+28/62	B;			+	+	+	+			+	+			+
Khalil N, et al. Neuropsychology 2009[n]	83/51	B; BO;		+	+			+							
Walsh KS, et al. Occup Environ Med. 2010	358/-	B; Y;								+					
Seo J, et al. PloS One 2014[o]	31/34	NA	8.5				+								
Seo J, et al. Neurotoxicology 2015[o]	43/41	B;	7.9							+					
Ravibaku K, et al. Int J Occup Environ Med 2015	146/-	B;	13.2			+	-				(+)				
Fenga C, et al. J Prev Med Hyg. 2016	40/40	B;	4.3				+			+		+			+
Number of studies with + / -				5+; 8-	10+; 1(+); 5-	11+; 9-	12+; 1(+); 12-	12+; 7-	7+; 9-	8+; 1(+); 4-	11+; 1(+); 9-	15+; 5-	1+;	3+;	10+; 1(+); 4-

Differences between groups in neuropsychological performance/or differences related to exposure parameters: Large/ Statistically significant different (Red) Tendency/Near significant (blue) No difference (green). p <0.05+; p 0.05 -0.10 (+); p >0.10 -;

Type of exposure characterization: Blood (whole blood): B; BO: bone; H: hair; Y: year. Duration of exposure (presented as hours in some studies), but calculated as mean years of exposure.

Notes

a. No significant differences between groups (except for neuroticism; EPI-C), although such differences are present within the exposed group.

b. Exposed subjects and controls were examined before and two years after entering work.

c. Referents were slightly older and better educated than exposed workers. Prospective study. Baseline results are given.

d. The participants are the same as in the study by Baker et al. 1983. In this paper, results after one year are given.

e. The participants are the same as in the study by Baker et al. 1983. In this paper, results after two year are given. Significant exposure-response relationships are shown. Evaluation after reduction of exposure showed improvement in POMS.

f. The authors performed a discriminant analysis in order to find the best combination for detection of neurotoxic effects from lead exposure.

g. Participants were classified as having medium (n=13) and low lead exposure (n=18) and were tested four times over a year, with further classification being made depending on changes in blood levels.

h. Finger tapping test was evaluated on four separate occasions.

i. Effects studied in two subgroups with previous high=28 or low=26 exposure; and current low exposure.

j. Effects studied in two subgroups with previous high and current high = 40 and low =40 exposure.

k. Longitudinal study.

l. Currently exposed workers =47 and former workers=48 were compared.

m. Exposed workers divided in medium=33 and low exposure=28.

n. A cohort re-examined 22 years later.

o. Neuropsychological tasks were performed during fMRI.

References Lead

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4.3 Manganese

Manganese (Mn) is the fifth most abundant metal in the natural environment, comprising about 0.1 % of the earth's crust. It is a silvery-grey metal resembling iron. Manganese (specific gravity 7.2–7.4) occurs in almost all types of soil. Metallic manganese is mainly used in steel production to improve hardness, rigidity, and strength. Manganese is also used in fungicides (maneb/mancozeb). Manganese has also been used as a fuel additive to increase the octane level of gasoline, but this use is currently limited in scope in "the developed world" (Lucchini et al. 2015).

Manganese is an essential trace element, but also a neurotoxicant (Bast-Pettersen et al. 2004). The human body contains about 12 mg of manganese, mostly in the bones. The principal source of exposure to manganese in subjects not occupationally exposed to manganese is the diet. Variations in manganese intake can to a large extent be explained by differences in nutritional habits. The highest concentrations of manganese occur in nuts, grains and vegetables. The intake increases in populations with high consumption of tea. The absorption rate in the gastrointestinal tract is rather low (3–5%). However, the amount of manganese absorbed is dependent on the subject's iron status. Iron deficiency increases the gastrointestinal uptake. The interdependence of iron and manganese may be explained by the fact that iron and manganese are absorbed by the same transport system. Both manganese in the form of Mn^{2+} and iron in the form of Fe^{2+} are bound by serotransferrin and compete for binding to this protein in the body (Lucchini et al. 2015). It has been suggested that manganese crosses the blood-brain barrier via the iron-transport system. Manganese is rapidly cleared from the brain, and increased levels of Mn are not necessarily found in brain tissue affected by Mn. In humans with Mn-intoxication, damage to nerve cells has been observed mainly in globus pallidus, and often in the striatum and subthalamic nuclei (Ellingsen et al. 2008).

High, long-term occupational exposure can cause manganism. In the International Classification of Diseases (ICD 10) manganism is classified as T 57.2. The onset of the disease is described as involving neurological and psychiatric signs and symptoms. The end stage, first described by Couper (1837), involves severe neurological impairment affecting mainly the motor system. Manganism has been reported to progress gradually, often with psychiatric symptoms and dystonia, but also with motor deficits similar to symptoms and signs observed in idiopathic Parkinson's disease (PD) (Calne et al. 1994).

Parkinson's disease versus manganism:

Parkinson's disease is a progressive, degenerative disorder that mainly affects the motor system. In 1817, the physician James Parkinson described five patients with "shaking palsy". The disorder is now recognized by his name.

In Parkinson's disease, four motor symptoms are considered to be cardinal: rest tremor, slowness of movement (bradykinesia), rigidity, and postural instability. The first sign is often a hand tremor at rest, and typically appears in only one hand (asymmetry). Parkinson's disease is a relatively common disorder that is associated with a 1–2 % lifetime risk of developing the condition (Olanow 2004).

The motor symptoms of Parkinson's disease are the result of reduced dopamine concentrations in the brain's caudate and putamen as a result of the degeneration of dopamine neurons in the substantia nigra pars compacta (SNc). In the early stages, the clinical symptoms of Parkinson's disease are significantly alleviated by levodopa (L-dopa) therapy. Levodopa is the precursor substrate for the synthesis of dopamine, the chemical that is decreased in Parkinson's disease (Guilarte 2010).

Unlike sufferers of Parkinson's disease, subjects with manganism display gait and balance dysfunction, speech impairment, and little if any response to levodopa. The manganese-induced motor dysfunction is not lateralized, and manganism patients suffer rest tremor to a lesser degree.

It has been discussed whether exposure to manganese could cause Parkinson's disease, but this theory seems to have been abandoned (Olanow 2004; Guilarte 2010).

Occupational exposure to manganese

The largest manganese resources are found in South Africa, China, Australia, Gabon, Brazil and India. The mining of manganese ore occurs in shallow underground mines or open pits. The main industrial use of manganese ores is in the production of ferromanganese (FeMn) and silicomanganese (SiMn). Norway has taken advantage of its hydro-electrical resources to develop one of the most important ferroalloy industries in the world. Norway has processing plants at Sauda, Kvinesdal and Porsgrunn.

Steel welders are exposed to manganese due to the addition of manganese alloys to improve the hardness and strength of the steel. Other occupational exposures involve dry alkaline battery manufacturing, glass production, manganese oxide and salt production. In order to protect workers from adverse neurological effects, SCOEL has recommended occupational exposure limit values in air; 0.2 mg/m^3 (inhalable fraction) and 0.05 mg/m^3 (respirable fraction) respectively (SCOEL 2011).

Occupational exposure limit values (Sweden): 0.2 mg/m^3 (inhalable fraction) and 0.05 mg/m^3 (respirable fraction) (Arbetsmiljöverkets författningssamling (AFS) 2018:1.

Neuropsychological effects in workers exposed to manganese

Altogether, 603 papers were identified in the literature search. Among these, 109 were selected for further evaluation. Forty studies were found to fulfil the inclusion criteria and included in the table. Studies only with symptom reporting, for instance Sjögren et al. (1990), were not included. Among studies not included were those where the subjects were involved in a litigation process, when this was clearly stated in the article, for instance the study by Bowler et al. (2003) covering 81 welders from different welding shops and industries in Texas. Neither did we include studies of 43 San Francisco Bay Bridge welders (Bowler et al. 2007) a. Subjects from that study are also presented in Bowler et al. 2007 b; and by Bowler et al. 2011. Such studies are at a risk of reporting response distortion especially in cases of subtle injuries (van Hout et al. 2003). Neither did we include studies of residents living in communities where environmental exposure to occurred.

In a meta-analysis including eight epidemiological studies of manganese-exposed workers, the slowing of responses was the most distinct finding. The speed of simple repetitive and sequential movements was reduced, but only one tremor variable was affected; a more discoordinated tremor was found in the exposed workers. (Meyer-Baron et al. 2013).

Few epidemiological, neuropsychological studies of manganism patients are available. In a study in which patients diagnosed with manganism were examined with a neuropsychological test battery and subsequently compared to a group of patients with idiopathic Parkinson's disease, several differences between the two groups were observed. Patients with manganism had severe bradykinesia and balance disturbances, but only slight postural tremor. In contrast, patients with Parkinson's disease had significant postural tremor and bradykinesia, but only slight balance disturbances. The patients with Parkinson's disease showed lateralized impairments (one foot or hand performed better than the other in different neurobehavioral tests). There was no indication of lateralized impairment for the manganism patients (Ellingsen et al. 2019).

Conclusion

When summing up the results in table 3, manual dexterity, tremor, other motor skills together with speed of information processing are the most dominant findings. Several studies report subjective symptoms. Memory problems or signs of intellectual impaired function are rarely found. The findings indicate that persons exposed to manganese tend to have problems with motor functions rather than cognitive function. This is in line with the meta-analysis by Meyer-Baron et al. (2013). This is also in line with the finding in the study of patients diagnosed with manganism (Ellingsen et al. 2019), where these functions, together with a slower reaction time and attention/working memory were the affected functions.

Table 3. Neuropsychological effects in workers exposed to manganese.

Epidemiological studies of exposed workers	N Expo/ referents	Type of exposure characterization	Years exposed	Verbal/ academic skills	Spatial skills/ perceptual organization	Speed information processing	Attention/ working memory	Verbal memory	Visual memory	Executive functions	Reaction time	Manual dexterity/ speed	Tremor	Other motor skills	Symptoms/ diagnosis
Roels H, et al. Am J Ind Med. 1987	141/ 104	Y; B; U;	7.1	+				+			+		+	+	+
Iregren A. Neurotoxicol Teratol. 1990[a] Wennberg A, et al. Scand J Work Environ Health. 1991[a]	30/ 60		9.9	(+)			(+)			-	+	+			+
Hua MS, et al. J Clin Exp Neuropsychol. 1991	17/19	Y; B; U;	11.9	-	-	-	-	-	-			-			
Roels HA et al. Br J Ind Med. 1992	92/ 101	Y; A; B; U;	5.3					-			+		+	+	-
Chia SE, et al. Scand J Work Environ Health. 1993	17/ 17	Y; A; B; U;	7.4			+	-		+			-	+	+	+
Mergler D,et al. Environ Res. 1994	115? 74/74	Y; A; B; U;	19.4	-		(+)	-			+	-	+	+	+	+
Lucchini R. et al. Scand J Work Environ Health. 1995[b]	61/ 87	Y; B; U;	11.8; - 13.8	+		+	+				-	+	+		
Sjögren B,et al. Occup Environ Med. 1996[c]	12/ 13	Y; B; U;	19.5	-		-	-				-	+		+	+
Hochberg F, et al. Neurology. 1996	27/ 32		>5									+	+	+	
Lucchini R. et al. Environ Res. 1997;	35/ 37	Y; A; B; U;	14.5										+	+	
Roels HA, et al. Neurotoxicology.1999[d]	24/ 39	Y; A;	13.5 (?)								+		+	+	
Lucchini R, et al. Neurotoxicology. 1999	61/ 87	A; B; U;	11?			+	+				-		+	+	+

Differences between groups in neuropsychological performance/or differences related to exposure parameters: Large/ Statistically different: Red; p <0.05+; Tendency/ Near significant: (Blue); p 0.05 -0.10(+); No difference: Green. p >0.10 -;

Type of exposure characterization: Duration of exposure (calculated as hours in some studies, but categorized as Year: Y; Air: A; Blood including whole blood (B), Serum (S) or Plasma (P); Urine: U.

(continuation) **Table 3. Neuropsychological effects in workers exposed to manganese.**

Epidemiological studies of exposed workers	N Expo/ referents	Type of exposure characterization	Years exposed	Verbal/ academic skills	Spatial skills/ perceptual organization	Speed information processing	Attention/ working memory	Verbal memory	Visual memory	Executive functions	Reaction time	Manual dexterity/ speed	Tremor	Other motor skills	Symptoms/ diagnosis
Crump KS, & Rousseau. Neurotoxicology. 1999	213/-	-; B; U;	>11					-			+		+		
Gibbs et al. Neurotoxicology. 1999	75/ 73	Y; A;	12.7								-	-	-	-	-
Myers JE et al. Neurotoxicology. 2003	509/ 67	Y; A; B; U;	18.2			+	+		(+)		-	+	-		
Bast-Pettersen R. et al. Int Arch Occup Environ Health. 2004	100/ 100	Y; A; B; U;	20.2	(+)		-	-		-	-	-	-	+	-	-
Yuan H et al. Life Sciences 2006	68/ 42	Y; A; B;	16			-	-		-		-	-		-	+
Bowler et al. Neurotoxicology 2006[e]	47		17.6-30.1	+	-	+	-	-	+	-		+		+	+
Blond M, Netterstrøm B. Neurotoxicology. 2007	51-53/ 97-106	Y; A; B;	24		(+)	-	-	-	-						
Blond M, et al. Neurotoxicology. 2007	60/ 14	Y; A; B;	24								-	-	-	-	
Bouchard M, et al. Am J Ind Med. 2007[f] Bouchard M, et al. Neurotoxicology. 2008[f] Park RM et al. Neurotoxicology. 2014[f]	77/ 81	Y; A; B; U;	15.3 /14.4			+	-		-	+		(+)	-	+	+
Ellingsen DG, et al. Neurotoxicology. 2008[g]	96/96	Y; A; B: U;	13.5			+	+					+	+	-	-
Cowan DM et al. Neurotoxicology. 2009	217/ 106	A; B;	-?						-			(+)	-	-	-

Differences between groups in neuropsychological performance/or differences related to exposure parameters: Large/ Statistically different: Red; p <0.05+; Tendency/ Near significant: (Blue); p 0.05 -0.10(+); No difference: Green. p >0.10 -;

Type of exposure characterization: Duration of exposure (calculated as hours in some studies, but categorized as Year: Y; Air: A; Blood including whole blood (B), Serum (S) or Plasma (P); Urine: U.

(continuation) **Table 3. Neuropsychological effects in workers exposed to manganese.**

Epidemiological studies of exposed workers	N Expo/ referents	Type of exposure characterization	Years exposed	Verbal/ academic skills	Spatial skills/ perceptual organization	Speed information processing	Attention/ working memory	Verbal memory	Visual memory	Executive functions	Reaction time	Manual dexterity/ speed	Tremor	Other motor skills	Symptoms/ diagnosis
Chang Y, et al. Neuroimage. 2010 Chang Y. et al. Neurotoxicology 2013	23-40/ 21-26	Y; A; B;	20.5	-		(+)/+	+	+	+	+		+			
Laohaudomchok W et al. Neurotoxicol. 2011	46/-	A;	>1								+	-		-	+
Summers MJ et al. J Clin Exp Neuropsychol. 2011[h]	103	A; -;	? (CEI)		-	+				+					
Sanchez-Ramos J et al. Int J Environ Res Public Health. 2011[i]	37/-	Y;	25.6										+		
Wastensson G et al. Int Arch Occup Environ Health. 2012	17/ 19	Y; A;	28.1									+	-	-	
Ellingsen DG et al. Neurotoxicol Teratol. 2014[j]	137/ 137	Y; A; B; U;	16.6			+	+				+	+		-	+
Ellingsen DG, et al. Neurotoxicology. 2015	63/ 65	Y; A; B; U;	19.5			-	-					+	+	+	+
Hassani H et al. Ind Health. 2016[k]	58/ 30	Y; A; B; U;	7.0/ 9.2						+	+	+				+
Seo J et al. Neurotoxicol Teratol. 2016[l]	53/ 44	Y; A; B;	16.7							+					
van Thriel C et al. Arch Toxicol. 2017	50/ 28	Y; A; B;	-							-	-				
Pesch B et al. Ann Work Expo Health. 2017	990?/ -	Y; A; B;	20									+	-	+	
Number of studies with + / -				3+ /2(+)/4-	0+ /1(+) /3-	11+ /1(+) /6-	7+ /10-	2+ /5-	4+ /1(+) /6-	6+ /4-	9+ /10-	14+ /2(+) /7-	12+ /7-	14+ /9-	14+ /5-
Epidemiological patient study:															
Ellingsen et al. Int Arch Occup Environ Health 2019[m]	34/ 43	Y; B; U;	23.7*			+	+				+	+	+	+	+

Notes

a. Iregren A. 1990 and Wennberg A, et al. 1991: The results were published in two different journals in 1990 and 1991.

b. Lucchini R. et al. Scand J Work Environ Health. 1995: The control group performed much better in a test of vocabulary, indicating that the control group was not adequate for comparison.

c. Sjögren B, et al. Occup Environ Med. 1996: Only 12 manganese exposed welders, almost a case study.

d. Roels HA, et al. Neurotoxicology. 1999: This is an 8-year follow-up study of Roels et al. 1987.

e. Bowler RM et al. Neurotoxicology 2006: The subjects were patients/had mental, medical, and neurological complaints that prompted referrals for a comprehensive evaluation. It is unclear whether they were also involved in a litigation process. There are doubts as to whether they ought to be included in the table.

f. Bouchard M, et al. Am J Ind Med. 2007; Bouchard M, et al. Neurotoxicology. 2008, and Park RM et al. 2014, are all follow-up studies of the Mergler et al. 1994 study.

g. Ellingsen DG, et al. Neurotoxicology. 2008 also included a group of patients with manganism. Their results are shown in the 2019 study.

h. Summers MJ et al. J Clin Exp Neuropsychol. 2011: in the study, the individual CEI is calculated, but no information about the year of exposure etc is given.

i. Sanchez-Ramos J et al. Int J Environ Res Public Health. 2011: The study has several methodological weaknesses, including self-selection.

j. Ellingsen DG et al. Neurotoxicol Teratol. 2014: The study comprises subjects from the 2008 study, but with a larger group; N= 137 subjects in each group.

k. Hassani H et al. Ind Health. 2016: The control group were office workers, which might make them a less than adequate reference group.

l. Seo J et al. Neurotoxicol Teratol. 2016: The finding of impaired executive functions in the exposed group is confusing, as the welders had the same problems with the subtest "color" as with the subtest "color of color word", indicating that the problems were in interpreting the colours, and not the "Stroop effect".

m. Ellingsen et al. Int Arch Occup Environ Health 2019 is a study of former welders who have developed manganism. Their results are compared with a control group. A group of patients with idiopathic Parkinson disease is also included in the study, but not shown here.

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4.4 Inorganic mercury

Mercury occurs as elemental mercury as well as inorganic and organic mercury compounds. Elemental mercury, or quicksilver, is a highly volatile silver-white metal that exists as a liquid or vapour (Hg^0) at room temperature. Mercury (Hg) occurs naturally in the environment, most of it being released from the earth's crust and the oceans into the atmosphere. However, a considerable amount is also released into the environment by human activities. A question of great concern is the accumulation of organic mercury (methylmercury) in the food chain (fish food) owing to transformation from inorganic nercury by microbial activity in polluted areas (Berlin et al. 2015). The main source of exposure to mercury for the general population is release of mercury vapour from dental amalgam, if present (Berlin et al. 2015).

After inhalation of mercury vapour, it is readily absorbed through the alveolar membrane into the blood, and about 80% is retained (WHO, 2003). Mercury vapour is oxidised to divalent mercury (Hg^2+) in the red blood cells and other tissues by the hydrogen peroxide–catalase pathway (Clarkson & Magos, 2006). However, mercury vapour dissolved in the bloodstream may cross the blood–brain barrier prior to oxidation and thus enter the brain. After entering the brain, mercury vapour is oxidized to Hg^2+, which is assumed to be the proximate toxic agent, exerting its action by attaching to thiol groups present in most proteins (Clarkson & Magos, 2006). Although little is known of the exact pattern of mercury distribution in the CNS in humans (Clarkson & Magos, 2006), the extent of and variety in neuropsychological impairment following Hg^0 exposure suggest that most structures in the CNS are affected. After exposure, most of the mercury in the brain is cleared with a short half-life, but a fraction may have a much longer half-life of several years (Clarkson & Magos, 2006). Excretion occurs via urine and faeces, with a whole-body half-life of about 60 days (Clarkson & Magos, 2006).

Exposure to mercury vapor may cause adverse effects in many organs, and the central nervous system and kidneys are considered the critical organs in humans (Berlin et al. 2015). The earliest symptoms and signs of mercury poisoning include a neurasthenic syndrome, with unspecific symptoms such as weakness, fatigue, and anorexia, called micromercurialism. The syndrom may appear in the case of occupational exposure to mercury concentrations in air of > 0.1 mg/m^3 (Berlin et al. 2015). Micromercualism has not been reported at concentrations <0.01 mg/m^3. At high exposure levels, a typical sign is a fine tremor interrupted by coarse shaking movements, initially involving the hands (Berlin et al. 2015). The tremor is intentional but becomes postural in more severe cases (Clarkson & Magos, 2006). Erethism, characterised by severe behavioural and personality changes, increased excitability, loss of memory, insomnia and depression may finally occur (Berlin et al. 2015).

Occupational exposure

Mercury has been used by mankind since ancient times for such purposes as the preparation of red ink and in medical applications (Goldwater 1972). Occupational use of mercury in mirror making in Venice was described by Ramazzini in his classic monograph "Diseases of Occupations" (Ramazzini 1713/1964). In modern time, occupational exposure occurs in mercury mines and chloralkali plants, in the manufacture of thermometers, fluorescent lightbulbs, and batteries, and in dentistry. Biological monitoring of exposure to mercury in the Swedish chloralkali industry over 40 years has shown substantially reduced exposure over time due to preventive actions (Sällsten et al. 1990).

Nowadays, almost all uses of inorganic mercury for industrial and dental purposes have been discontinued in Sweden since a general ban was passed into law in 2009. However, exposure to inorganic mercury may occur in the recycling industry, in workers involved in the collection, transportation, and recycling of EEE-waste (Julander et al. 2014).

Inhalation of Hg^0 is the common route of exposure to mercury from occupational sources (WHO, 2003). Recent mercury exposure is reflected in blood and urine. Blood samples are most useful in relation to short-term exposure at higher levels (WHO, 2003). Mercury in blood reflects both organic mercury (from fish) and inorganic mercury (for example from amalgam) and is expected to be 0.3–3.5 µg Hg/L blood in the general population in Sweden (Sällsten and Barregård 2014). However, urine samples are considered being the best indicator of body burden from long-term exposure to elemental mercury (WHO, 2003). Mercury concentration in urine may be affected by hydration; therefore, it is normally corrected for creatinine and expressed as µg/g creatinine (µg/gC) (WHO, 2003). Levels of urinary mercury are expected to be 0.5–3 µg/gC in the general population (Sällsten and Barregård 2014).

SCOEL (2007) has recommended 10 µg Hg/L blood and 30 µg Hg/g creatinine in urine as biological limit values based on neurobehavioral toxicity appear at 35 µg Hg/g creatinine in urine. However, results from the meta-analysis by Meyer-Baron et al. (2002) indicate that adverse effects may begin at between 20–30 µg Hg/g creatinine in urine.

Occupational exposure limit value and biological limit value

The **occupational exposure limit value in air** is 0.02 mg/m3 (Arbetsmiljöverkets författningssamling (AFS) 2018:1). Those who are occupationally exposed to inorganic mercury are covered by a monitoring system involving periodic medical examinations, biological exposure control of the content of mercury in blood, and regulations dictating that they must discontinue work at high blood mercury levels. The blood limit value is 50 nmol/L (10 µg Hg/L) (Arbetsmiljöverkets författningssamling (AFS): 2019:3).

Neurotoxic effects in workers exposed to inorganic mercury

Altogether, 710 papers were listed in the initial search. 115 papers did not cover mercury and were excluded. 140 papers were selected for further evaluation. Five papers only reported symptoms and were thus not included. In total, 37 papers fulfilled the inclusion criteria and were included in table (4). All papers were studies carried out on groups of workers with occupational exposure to inorganic mercury. The papers by Kishi et al. from 1993 and 1994 respectively were duplicates. Six papers reported results from neuropsychological testing after the cessation of exposure (Albers et al. 1988; Kishi et al. 1993; 1994; Mathiesen et al. 1999; Letz et al. 2000; Bast-Pettersen et al. 2005).

When summing up the results from the table, a clear tendency towards positive rather than negative findings of tremor and manual dexterity is seen. For the other neuropsychological domains, either fewer positive than negative findings, or as many positive as negative findings, are seen, with the exception of spatial skills.

Thirteen out of twenty studies reported increased tremor or changes in tremor parameters, as assessed with hole-tremormeters or accelerometers, or both. Thirteen out of twenty-one studies reported decrements in manual dexterity and speed in exposed workers in various tests such as finger tapping (Langolf et al. 1978; Ngim et al. 1992; Liang et al. 1993; Kishi et al. 1993; 1994; Gunther et al. 1996; Echeverria et al. 1998; Haut et al. 1999; Frumkin et al. 2001), the Grooved Pegboard test (Mathiesen et al. 1999; Haut et al. 1999; Powell et al. 2000; Frumkin et al. 2001), and Santa Ana dexterity or similar pegboard test (Piiviki et al. 1984; Kishi et al. 1993; 1994). Among other motor skills, inferior performance among exposed workers was found in different tests of hand-eye coordination (Roels et al. 1989; Letz et al. 2000; Kishi et al. 1993; 1994), the Catsys Coordination test (Netterström et al. 1996), and Sway (Iwata et al. 2007).

In a meta-analysis by Meyer-Baron et al. (2002), inferior motor performance in tapping, Grooved Pegboard and Purdue Pegboard was found in exposed subjects compared to controls. Some effects were also seen on attention, visual memory and spatial skills. In a subsequent meta-analysis, a larger impairment of motor performance than of other domains such as memory and attention was demonstrated (Meyer-Baron et al. (2004). Rohling et al. (2006) performed a meta-analysis comprising 36 studies and found that the greatest impact from Hg exposure was on psychomotor skills. Tests for tremor were not included in these meta-analyses.

In a recent systematic review by Field et al. (2017), the results from 45 studies including physical examination, neurobehavioral, and neurophysiological tests on workers currently exposed to Hg are reported. In this study, dose-relatedness was shown for tremor (strongest for postural tremor) and motor function for tests of dexterity and motor speed. None of these effects were shown using **physical examination** at Hg levels < 200 μg/L in urine, or when using **neurobehavioral testing** at Hg levels <20 μg/L in urine.

Conclusion

Our findings indicating that inorganic mercury predominantly affects manual dexterity and other motor skills, including tremor, are in line with the meta-analyses by Meyer-Baron et al. (2002 and 2004), Rohling et al. (2006). Tremor is one of the earliest signs of mercury intoxication and can be demonstrated using neurobehavioral tests at Hg levels >20 μg/L in urine (Fields et al. 2017). Effects on other neuropsychological domains could not be shown in our review.

Table 4. Neuropsychological effects in workers exposed to inorganic mercury.

Epidemiological studies of exposed workers	N Expo/ referents	Type of exposure characterization	Years exposed	Verbal/ academic skills	Spatial skills/ perceptual organization	Speed information processing	Attention/ working memory	Verbal memory	Visual memory	Executive functions	Reaction time	Manual dexterity/ speed	Tremor	Other motor skills	Symptoms/ diagnosis
Langolf GD, et al. Am Ind Hyg Assoc J. 1978	79/51	U;	NA		(+)							+	+		
Williamsson AM, et al. IAOEH. 1982	12/12	U;	NA			-	+	-			-		+		
Fawer RF et al. Br J Ind Med 1983	26/25	A; U; B;	15.3										+		
Smith et al. Br J Ind Med. 1983	28/26/60/-	U;	NA				+								
Piivkivi L et al. Scand J Work Environ Health. 1984	36/36	Y; U; B;	16.9	(+)	-		-		-			+#			
Roels H et al. Am J Ind Med. 1985[a]	185/ 162	Y; B; U;	4.8/7			-	-				-		+		
Verberk et al. Am Ind Hyg Assoc J. 1986*	21/-	U;	0.5–19										+		
Albers JW et al. Ann Neurology 1988[b]	247/ 255	U;	NA										+		
Piiviki L, et al. Scand J Work Environ Health. 1989[c]	60/60	B; U;	14		-	-		-	-			+			+
Roels H, et al. Environ Research.1989[d]	54/48	B; U;	7.7										+	+	
Soleo L, et al. Br J Ind Med. 1990	8+20/22	Y; A; U;	10.3/ 12.4			-	+		-		-	-			
Chapman LJ, et al. Br J Ind Med. 1990	18/18	U;	5.3										+		
Ngim CH. et al. Br J Ind Med. 1992	98/54	Y; A, B;	5.5	-	+	+	+		+			+			
Langworth S, et al. Br J Ind Med. 1992	89/75	U; B;				-	-				-	-	-		+

Differences between groups in neuropsychological performance/or differences related to exposure parameters: Large/ Statistically different (Red) Tendency/Near significant (blue) and no difference (green). p <0.05+; p 0.05 -0.10 (+); p >0.10 -; # indicate better performance in the exposed compared to control groups.
Type of exposure characterisation: Duration of exposure (calculated as hours in some studies, but categorized as Year: Y; Air: A; Blood (B); Urine: U.

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Liang YX et al. Environ Research. 1993	88/70	Y; A; U;	15.8	+	+	-	+	-	-			+			
Kishi R et al. Environ Research. 1993[b] Kishi R et al. Occup Environ Med 1994[b]	76/76	Y; A; U;	18		+	+	+				+	+		+	
Echeverria D. et al. Neurotoxicol Teratol 1995.	19/20	U;	25	+		-	-			-	-	-			+
Ritchie KA et al. Occup Environ Med 1995.	39/40	U;	NA	+	+	+	+	+	-		+				-
Netterström B, et al. Neurotoxicol Teratol 1996	7+7/15	U;	NA										+	+	
Gunther W, et al. Neurotoxicology 1996	14–21/34–50/37–43	U;	11.8/12.7				-	-	-		-	+			-
Bittner NH, et al. Neurotoxicol Teratol 1998*	230/-	U;	NA				-					-	+		
Echeverria D et al. FASEB J 1998	34+17/-	U;				-			+	+		+	-		+
Mathiesen T, et al. Scand J Work Environ Health 1999[b]	75/52	Y; U;	7.9	-		-	-	-	+	-	-	+	-		
Haut MW, et al. Appl Neuropsychol 1999[e]	13/13	A; B;	2–4 w	+	+	+	-	+	-	+		+		-	
Biernat H, et al. Neurotoxicology 1999.	63/17	U;	NA										+		

Differences between groups in neuropsychological performance/or differences related to exposure parameters: Large/ Statistically different (Red) Tendency/Near significant (blue) and no difference (green). p <0.05+; p 0.05 -0.10 (+); p >0.10 -; # indicate better performance in the exposed compared to control groups.
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Letz R, et al. Neurotoxicology 2000[b]	104/101	Y; U;	4.8	-		-		-		-			(+)	+	
Powell TJ, et al. Brain injury 2000[b]	15/15	NA	2.5	-	-	+	+	-	-	-		+			-
Frumkin H, et al. Am J Ind Med 2001[b]	147/132	Y; U;	5.73		+	-	-	+		-	-	+	+	-	+
Ellingsen DG, et al. Neurotoxicology 2001	47/47	Y; U;	13.3	-		+	-		+			-	-		
Bast-Pettersen R, et al. Neurotoxicology 2005[b,f]	49/49	Y; U; B;	13.1	-		-	-		-	-		-	-		-
Iwata T, et al. Int Arch Occup Environ Health 2007	27/52	U;											+	+	
Wastensson G, et al. Neurotox teratol 2006	43/22	Y; U;	15										-		-
Wastensson G, et al. Neurotoxicology 2008	43/22	Y; U;	15									-		-	
Zachi EC, et al. Dementia Neuropsychol 2008[b,g]	13/-	-	7.4	-	-		+	-	-	+		-			
Al-Batanony MA, et al. Int J Occup Environ Med 2013	138/151	A; U;	NA	+		+	+		+						
Milioni AL, et al. Neurotoxicology 2017	31/20	Y;	11				+		+	-					
Exposed workers Number of studies with + / -				5+;1(+);6-	7+;1(+);4-	7+;12-	11+;12-	3+8-	6+10-	3+7-	2+8-	11+8-	13+; 1(+); 6-	5+;3-	5+;5-

Differences between groups in neuropsychological performance/or differences related to exposure parameters: Large/ Statistically different (Red) Tendency/Near significant (blue) and no difference (green). p <0.05+; p 0.05 -0.10 (+); p >0.10 -; # indicate better performance in the exposed compared to control groups.
Type of exposure characterisation: Duration of exposure (calculated as hours in some studies, but categorized as Year: Y; Air: A; Blood (B); Urine: U.

Notes

a. Roels H et al. Am J Ind Med. 1985. Effects on hand tremor spectrum recorded with an accelerometer were shown in Hg-exposed male workers, but not female workers.

b. Studies of workers with previous Hg-exposure (after cessation of exposure).

c. Piiviki et al. Scand J Work Environ Health. 1989.. Exposed workers reported significantly more memory disturbances and sleep disorders than referents, but performed better on the eye-hand coordination test. Strain caused by shift work was considered a possible cofactor for other increased subjective symptoms.

d. Roels H et al. Environ Research.1989. The hole tremormeter was affected, but no statistically significant changes in tremor measured by an accelerometer.

e. The control group was recruited via advertisement from a similar community.

f. Performance in the Digit Symbol test improved after cessation of exposure in the subjects with the highest B-Hg concentrations.

g. Zachi EC, et al. Dementia Neuropsychol 2008. Patients diagnosed with micromercurialism and examined 18 months earlier. Performance at re-examination was compared with performance at baseline. Former workers performed better on the Wisconsin test, which indicates improved executive functions, but performed significantly worse in a test of immediate attention (Digit Span).

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4.5 Carbon monoxide

Carbon monoxide (CO) is a colourless and odourless gas. It occurs in the atmosphere due to emission from natural sources or produced by human activities such as incomplete combustion of carbon and carbon compounds, for example in gasoline engines when there is insufficient oxygen for carbon dioxide (CO2) to be formed. CO is an important industrial gas used in the production of chemical intermediates. The most important sources of exposure outside the workplace are car exhaust fumes and tobacco smoke. (Stockmann-Juvala 2012).

After inhalation, CO diffuses from the alveoli of the lungs to the blood, and the red blood cells. The mechanisms of carbon monoxide poisoning mean that CO, which binds stronger than oxygen to haemoglobin (Hb), displaces the oxygen from the haemoglobin molecules, causing carboxyhaemoglobin (COHb) to be produced, and thereby inducing oxygen deficiency in various organs, a sequence described in the 1800s by Claude Bernard (Bernard 1865). COHb is usually expressed as % of total Hb.

CO is also naturally formed in the body during various metabolic processes, and acts as a neurotransmitter, but this production gives a content of COHb (carboxyhaemoglobin) of 0.4– 0.7%. Non-smokers typically have COHb levels up to 2%, while smokers may have COHb levels up to 5%. Levels over 9% indicate exogenous carbon monoxide exposure, even among smokers (Hampson, 2018).

Acute effects related to CO exposure cover a wide range of symptoms, such as shortness of breath during vigorous exercise and dilation of cutaneous blood vessels at 10%, to more severe symptoms such as headache, dizziness, disturbed judgement, dimness of vision at COHb 30%. COHb levels of 50–60% are often lethal (Stockmann-Juvala 2012). Treatment for CO poisoning includes removal from the site of exposure and administration of supplemental oxygen, and in severs cases hyperbarivc oxygen (HBO). Lower concentrations (5–10%) can be harmful to people with ischemic heart disease (Klaassen, 1995). No health effects have been observed at levels below 2% (Costa et al, 1995). A foetus is at higher risk than a healthy adult because of higher CO haemoglobin affinity (Stockmann-Juvala 2012), and it is therefore vital that pregnant women are not exposed to high levels of CO.

Occupational exposure

Exposure to CO is common in many occupational areas, including those associated with vehicle exhaust fumes. In the workplace, high CO exposure occurs mainly in steel production and other processes during which carbon compounds are heated and gasified.

Carbon monoxide is normally found in low levels in welding fumes (Sjögren 2013). However, in the case of gas welding, especially in confined spaces and in district heating pipes, carbon monoxide levels may be high and have even caused deaths (Antonsson et al. 2013). Even with Metal Active Gas (MAG) welding where carbon dioxide is used as a protective gas, it is possible to be exposed to high levels of carbon monoxide. In this type of welding, the carboxy-haemoglobin level in the blood has been 20 percent

(De Kretser et al. 1964). When welding with propane gas, the risk of high levels of carbon monoxide increases further. In arc-air gouging with carbon electrode, the air content of carbon monoxide can reach levels of 100 ppm, which are higher than the hygienic limit value. A short-term limit/ excursion limit (STEL) (15 mins) of 100 ppm (117 mg/m^3) is set in order to limit accumulation of COHb (see below). Changes in CNS activity start to increase at 5% COHb, indicating that a limit value should not produce a COHb concentration>4%, which corresponds approximately to 30 ppm (35 mg/m^3) (SCOEL 1995).

The occupational exposure limit values for carbon monoxide are 20 ppm (23 mg/m^3) as an 8-hour TWA and a short-term limit/ excursion limit (STEL) of 100 ppm (117 mg/m^3) (Arbetsmiljöverkets författningssamling (AFS) 2018:1).

Neuropsychological effects following exposure to carbon monoxide

In the present literature search, a total of 575 papers were listed in the initial search. 54 studies were selected for a further evaluation. Only 7 papers fulfilled the inclusion criteria and were included in the final literature review. Of the papers included, 5 studies covered neuropsychological effects in patients after acute CO poisoning compared to a referent group (Rottman et al. 1995; Descamps et al. 2002; Chen et al. 2013, Pages et al. 2014; Yang et al. 2015) and one study compared neuropsychological performance between patients with acute and delayed CO poisoning (Yeh et al. 2014).

Rottman et al. (1995) performed testing before and after treatment with Hyperbaric Oxygenation (HBO), and made comparisons with a control group. Both groups improved in performance when retested.

In the study by Deschamps et al. (2003), patients lacking other risk factors for cognitive impairment and treated for CO poisoning one month earlier were compared to paired controls. The patients performed similar (or even better in some tests) in tests on working memory and attention, long term memory and learning, processing speed and reaction time than controls.

Chen et al. (2013) conducted MRI and neuropsychological tests on 11 patients with delayed encephalopathy, 11 patients with acute CO poisoning and 15 controls. Exposed subjects performed worse on tests assessing spatial skills, speed of information processing, and executive functions.

Pages et al. (2014) investigated patients with CO poisoning following a natural disaster (storm) and reported decrements in tests assessing processing speed, verbal episodic memory, working memory, and executive functions compared to paired controls. The patients scored higher than controls on two subtests (major depression and PTSD) in MINI (mini-international neuropsychiatric interview) (Sheehan et al. 1998).

Yang et al. (2015) compared cognitive performance in patients after CO poisoning and a control group and found worse performance in all domains assessed (attention, memory, execute function). After 6 months, most cognitive functions were significantly improved, except for a test assessing executive function (Wisconsin Card Sorting Test).

Yeh et al. (2014) compared performance in patients with acute and delayed CO poisoning after one and six months. Patients with delayed syndrome performed worse on psychomotor speed, visual-spatial ability, language, verbal and working memory, and executive function than those with acute poisoning at 1 month and had more significant progress at 6 months. Mini Mental State Examination (MMSE) (Folstein et al. 1975) and the Cognitive Abilities Screening Instrument (CASI) (McCurry et al. 1999) were used as indicators of general cognitive function.

The paper by Amitai et al. (1998) reports an experimental study investigating effects of acute low-level exposure to CO on healthy volunteers exposed to CO for 1.5–2.5 hours (mean air CO 61±24 ppm) compared to a control group. Neuropsychological assessment after exposure revealed lower scores for the exposed group in tests measuring executive functions, attention/working memory, processing speed, long-term memory, and spatial skills.

Watt et al. (2018) performed a meta-analysis including studies between the years 1995 and 2016 to examine differences in neuropsychological functioning in patients with CO poisoning compared to healthy controls. Data from all studies were pooled to determine standard mean differences using a random-effects model. In general, healthy controls performed significantly better than CO-poisoned participants in the domains of divided attention, immediate memory, and processing speed. Performance for the domains of sustained attention, recent memory, visuospatial/constructional abilities, and working memory was significantly improved over time after initial exposure.

Conclusions

When summing up the table, CO poisoning seems to affect various neuropsychological domains, although some differences are seen for attention/working memory and processing speed, for which we see more positive findings than negative ones. Tests for spatial skills and visual memory were used in three studies, all with positive findings. However, few studies were included in the table, and none of them applied tests on motor skills. Our results regarding attention/working memory and processing speed are supported by the findings in the recent meta-analysis by Watt et al. (2018).

Table 5. Neuropsychological effects in humans exposed to carbon monoxide.

Epidemiological studies of exposed workers	N Expo/ referents	Type of exposure characterization	Years exposed	Verbal/ academic skills	Spatial skills/ perceptual organization	Speed information processing	Attention/ working memory	Verbal memory	Visual memory	Executive functions	Reaction time	Manual dexterity/ speed	Other motor skills	Symptoms/ diagnosis
Rottman SJ, et al. Prehosp Dis Med. 1995[a]	35/20			-	-	-	-			-				
Deschamps D, et al. Occup Environ Med. 2003[b]	32/32	B;				-#	-#	-#		-	-#			
Pages B, et al. BMC Neurol. 2014[c]	38/38			-		+	+	+		+				-
Yeh ZT, et al. Appl Neuropsychol Adult. 2014[d]	11+14/-				+	+	+	+	+	+				+
Chen HL, et al. BMC Neurology 2013[e]	11+11/15				+	+				+				
Yang et al. Psychiatry Res. 2015[f]	21/31						+	+	+	+				
Experimental study														
Amitai y, et al. Arch Neurol. 1998[b]	45/47	A; B;	1.5–2.5 hours		+	+	+	-	+	-				
Number of studies with + / -				2-	3+;1-	4+; 2-	4+; 2-	3+; 2-	3+;	4+; 3-	1-			1+; 1-

Differences between groups in neuropsychological performance/or differences related to exposure parameters: Large/ Statistically different (Red) Tendency/Near significant (blue) and no difference (green). p <0.05+; p 0.05 -0.10 (+); p >0.10 -; # indicate better performance in the exposed compared to control groups.
Type of exposure characterisation: Air: A; Blood: B.

Notes

a. The exposed subjects were tested before and after HBO therapy.

b. Exposed subjects were patients examined one month after acute carbon monoxide intoxication.

c. Exposed subjects were patients examined 51 days after acute carbon monoxide intoxication.

d. Exposed subjects were patients with acute (ANS) (n=11) and delayed carbon poisoning (DNS)(n=14) examined 1 month and 6 months after therapy.

e. Exposed subjects were patients with acute (ANS) (n=11) and delayed carbon poisoning (DNS)(n=11) and 15 controls examined after 25 months.

f. Exposed subjects were patients examined after acute carbon monoxide intoxication and 6 months later.

g. Experimental study.

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4.6 Organic solvents

The term "organic solvents" is used to classify chemical compounds or mixtures used to "extract, dissolve or suspend" non-water-soluble materials such as fats, oils, lipids, cellulose derivatives, waxes, plastics, and polymers. Most of these solvents are volatile liquids at room temperature, and many of them pass easily through intact skin. They are lipophilic with an affinity for nerve tissue, are soluble in blood, and pass rapidly through the membranes of the lung (Bast-Pettersen 2009). The term "solvents" covers organic chemicals that differ widely in structure, and many common solvents are used as mixtures.

The main routes of exposure are inhalation and skin contact. After absorption, solvents may be exhaled unchanged, bio-transformed and then excreted, or accumulated in lipid-rich tissues such as the brain, myelin, and adipose (White and Proctor 1997). Exposure dosage depends on several factors including air concentration, solubility, and duration of exposure. Workers exposed to solvents work as painters, floor-layers, printers, industrial cleaners or in paint or glue manufacturing, for example. Due to improved working conditions, exposure levels are much lower today than they were in the 1980s. In Norway, it is estimated that exposure levels were roughly about 10 times higher in 1986 than in 2007, based on analyses from more than 11,000 samples of combined solvents (Bast-Pettersen 2009).

In contrast to several of the other substances described in this report, there is consensus regarding a diagnosis associated with exposure to solvents (van Valen et al. 2012). Long-term/high-grade exposure can lead to chronic solvent induced encephalopathy (CSE), a condition that develops slowly. The term CSE is often used synonymously with chronic toxic encephalopathy (CTE). Terms like organic solvent syndrome or chronic painter's syndrome have also often been used for this condition. CSE is characterized by symptoms such as irritability, fatigue, headache, sleep disturbances, lability of affect, lack of initiative, concentration problems, and memory complaints (Bast-Pettersen 2009; van Valen et al. 2012).

Neurobehavioral testing has played a central role in studying the adverse effects in humans exposed to neurotoxic substances at work (Anger 1990; 2014). The Nordic countries were among the first to study the effects of solvents on aspects of intellectual functioning such as memory and concentration (Spurgeon 2006). In 1976, Denmark became the first country officially to recognize the disease and began providing compensation for affected workers (Spurgeon 2006). A system of financial compensation has now been established in several countries for the benefit of employees diagnosed with CSE.

The "gold standard" for the diagnosis of CSE was set in the 1980s at two consensus meetings on criteria for the diagnosis of CSE.

The "Copenhagen meeting" (WHO 1985) agreed on the following classification:

The classification based on the "Copenhagen meeting" (WHO, 1985)
Type I: Organic affective syndrome
Type II: Mild chronic toxic encephalopathy
Type III: Severe chronic toxic encephalopathy

The "Raleigh (North Carolina) consensus meeting" (Cranmer & Golberg 1986) agreed on the following classification:

The classification based on the "Raleigh (North Carolina) consensus meeting" (Cranmer & Golberg, 1986):
Type 1: Symptoms only
Type 2A: Sustained personality or mood change
Type 2B: Impairment in intellectual function
Type 3: Dementia

In clinical practice, the diagnosis CSE has been used synonymously with the WHO type II or the Raleigh criteria type 2 B.

The WHO and Raleigh criteria only offer rough guidelines for classifying the severity of the cognitive impairment in CSE patients. In 2012, a European working group published a consensus document on the neuropsychological assessment of CSE (van Valen et al. 2012). Based on a literature review, the authors found that the most commonly observed neuropsychological impairments in CSE patients are within the domains of attention, particularly the speed of information processing, memory, and motor performance. The influence on memory processes mainly involves immediate recall.

The consensus group also looked at the severity of cognitive impairment and recommended a score based on effect size/impaired score be made for each test variable.

The consensus group recommended that test results lower than the 16th percentile and higher or equal to the 5th percentile were recoded as / considered to be moderately impaired, while test scores lower than 5th

percentiles were recoded as impaired (van Valen et al. 2012). The use of percentiles refers to the distribution of test results in a population of the same age, gender and education. Test results < 16th percentile are equivalent to normally distributed test results below -1 SD/-1 z-score/T40/ or the lower half of stanine 3. Test results < 5th percentile are equivalent to normally distributed test results below < -1.65 SD/-1.65 z-score/T32 or stanine 1. It is important to be aware of this consensus regarding the severity of the impairment, as in some fields of medicine an impairment of < 2.0 SD/< 2.0 z-score is required for being diagnosed with an impairment.

The consensus group also took into consideration the problems involved in differential diagnosis. "Major conditions affecting cognition should be recognized and treated, if possible, before a neuropsychological examination takes place. Examples of common treatable causes are sleep disorders, major depression, anxiety disorders, substance abuse and excessive use of CNS-affecting medication. ... In the presence of major irreversible diseases affecting cognition, CSE cannot be identified nor ruled out. … the possibility of a combined aetiology should be taken into account. … CSE and another pathological condition may coexist, and in general neuropsychological assessment alone cannot establish which condition is the main contributor to the neuropsychological impairment" (van Valen et al. 2012).

An issue that has been much disputed, concerns the amount of exposure required to produce detectable neurobehavioral effects. Several countries use 10 years of daily full-time exposure as a rough guideline. With high exposure, the exposure time can be shorter.

In a study of Finnish patients diagnosed with CSE, the diagnosed subjects had on average 28.4 years of exposure to solvents. However, when their exposure was calculated into Occupational Exposure Limit Years (OELY), the value was 10.5 years, with the lowest OELY four years. One Occupational Exposure Limit Year is equivalent to working eight hours a day for one year with solvent exposure at the level of the Finnish Occupational Exposure Limit, which was set in 1981, and which corresponds to the American Conference of Governmental Industrial Hygienists (ACGIH).

In clinical practice at the Finnish Institute of Occupational Health, six or more Occupational Exposure Limit Years is usually considered requisite for the diagnosis of CSE assuming that all other diagnostic criteria are met (Keski-Säntti et al. 2010). In a Norwegian study of CSE patients, the largest differences between exposed and referents occurred for the subgroup of patients that had been exposed for between 16 and 23 years (Bast-Pettersen 2009). The study covered patients diagnosed before 1990. This is important to bear in mind, because, as mentioned, exposure levels are, at least in the Nordic countries, much lower than before.

Conclusion

There are no consistent findings when summing up the results in table 6. In contrast to the other substances that are described in this report, the studies presented in the table of solvents are based on a previous literature review (Bast-Pettersen et al. 2013), not on the current literature review. However, the present report also includes studies of diagnosed CSE patients. The articles have been re-evaluated as the scoring criteria used in the present study are somewhat different and include more categories than the study by Bast-Pettersen et al. (2013).

The table shows that regarding the studies of exposed workers, for almost every function studied, there are as many positive as negative findings. This goes for speed of information processing, spatial skills, visual memory, reaction time, manual dexterity, and other motor skills. It could be stated that there was a small tendency towards impaired executive function, with five positive and three negative studies. Only a minority of the studies reported positive outcomes on tests of attention/working memory or verbal memory.

When looking at the five studies of patients with CSE, which can be regarded as the endpoint related to solvent exposure, impaired attention/working memory and speed of information processing were, with one exception, observed in the studies in which such tests were included. The results of the patient studies are in line with the findings of the European group (van Valen 2012).

Table 6. Neuropsychological effects in workers exposed to solvents.

Epidemiological studies of exposed workers	N Expo/ referents	Type of exposure characterization	Years exposed	Verbal/ academic skills	Spatial skills/ perceptual organization	Speed information processing	Attention/ working memory	Verbal memory	Visual memory	Executive functions	Reaction time	Manual dexterity/ speed	Tremor	Other motor skills	Symptoms/ diagnosis
Elofsson SA et al. Scand J Work Envir Health 1980[a]	80/ 80+80	Mixed Solv	CEI	-	+	+			+		+	+			+
Iregren A. Neurobehav. Toxicol.Teratol. 1982	34/34	Toluene Printers	16.3	-	-	-	-				+				
Anshelm Olson B et al. Neurobehav. Toxicol. Teratol. 1982	47/47	Mixed Solv Paint Ind.	4.4/24.1			+			+		+				+
Cherry N et al. Br J Ind Med. 1985 study A; Painters study B; Rubber	44/44 52/52	Mixed Sol Toluene	11.7 ?	+ +	+ -	+ -		+ -	+ -		+ -	+ -			+
Ørbaek et al. Scand.J.Work Environ.Health. 1985	50 /50	Mixed, Paint Industry	>10/CEI	-	-	+		-	-					-	
Ekberg K. et al. Br J Ind Med 1986	25/25	Toluene, Acetone, Benzene, Etyl acet	27+9	-	+	-			+			+			+
Mikkelsen S et al. Acta Neurol. Scand.Suppl. 1988	85/85	Mixed S/ White Sp	32.5	-	-	+	-	+	-	-				+	+
Lash AA et al. Br.J.Ind.Med. 1991	25/21	Methyl chloride	29.6		-	-	+#	-	-		-	-		-	
Fallas C et al. . Br J Ind Med 1992	60/60	Styrene	6.5			-	-		-		+	-		+	
Chia et al. Neurotoxicology. 1993	19/26	Mixed Sol	3.4			+	+		+			+			
Colvin et al., Environ.Res. 1993	43/24	Mixed Sol Paint Fact	?/CEI			-	-	-	+		+	-		+	-

Differences between groups in neuropsychological performance/or differences related to exposure parameters: Large/Statistically different: Red; p <0.05+; Tendency/Near significant: (Blue); p 0.05 -0.10 (+); No difference: Green. p >0.10 -; # The exposed subjects performed better, therefore the significant difference is counted as "-"

Type of exposure characterization: Duration of exposure (calculated as hours in some studies, but categorized as Year: Y;
CEI: Cumulative Exposure Index; Usually based on work history; job titles, years of employment.
OEL: Occupational Exposure Limit (Years);
The exposure is calculated in relation to the Occupational Exposure Limits.

(continuation) **Table 6. Neuropsychological effects in workers exposed to solvents.**

Epidemiological studies of exposed workers	N Expo/ referents	Type of exposure characterization	Years exposed	Verbal/ academic skills	Spatial skills/ perceptual organization	Speed information processing	Attention/ working memory	Verbal memory	Visual memory	Executive functions	Reaction time	Manual dexterity/ speed	Tremor	Other motor skills	Symptoms/ diagnosis
Daniell et al., Br.J. Ind.Med. 1993	43/31/ 39	Mixed Sol	CEI			(+)	-	-	(+)		-	-		-	-
Jegaden D et al. Int.Arch. Occup.Environ.Health. 1993	30/30	Styrene	CEI				-				+				
Bolla, K I et al. Am.J.Ind. Med. 1995	144 /52	Mixed Solv	15	+	+	+			+	+		+			(+)
Escalona E et al. AM J Ind Med 1995	67/82	Mixed Solv	7			+	-		-		+	+		-	+
Lundberg et al. Scand.J.Work Environ. Health. 1995	135/71	Mixed Solvents	? CEI		+	+	+	-	(+)	(+)	-	-			+
Tsai SY et al. Neurotoxicology and Teratology 1996	41/45	Styrene (Fiberglas	8.4	-		-	-	-	-		+	-		+	-
Daniell WE et al. Occup. Environ.Med. 1999	63+15 /123	Mixed Solvents	37/31	-	+	-	-	+	+	+	-	+			+
Viaene MK et al. Occup. Environ.Med. 2001[b]	27+90 /64	Styrene (Boat pr)	CEI			+	(+)	(+)		+	-			(+)	
Deschamps D et al. Int Arch Occup Environ Health 2001	72/61	Toluene	19.9	+#		-	-			-	-				+
Böckelmann et al. Disabil. Rehabil.2004;	84/85	Mixed Solv Car painters	16/ 13	+	-	+	+				+				+
Chouaniere, D. et al. Am.J.Ind.Med 2002	39 +89 /-	Toluene (Print-ing)	14/ CEI	-		-	+	-	-		-				-
Dick F et al. QJM. 2002;	78/42	Mixed S	?/ OEL			+		+	+	+	(+)		(+)	+	+

Differences between groups in neuropsychological performance/or differences related to exposure parameters: Large/Statistically different: Red; p <0.05+; Tendency/Near significant: (Blue); p 0.05 -0.10 (+); No difference: Green. p >0.10 -; # The exposed subjects performed better, therefore the significant difference is counted as "-"

Type of exposure characterization: Duration of exposure (calculated as hours in some studies, but categorized as Year: Y;
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(continuation) **Table 6. Neuropsychological effects in workers exposed to solvents.**

Epidemiological studies of exposed workers	N Expo/ referents	Type of exposure characterization	Years exposed	Verbal/ academic skills	Spatial skills/ perceptual organization	Speed information processing	Attention/ working memory	Verbal memory	Visual memory	Executive functions	Reaction time	Manual dexterity/ speed	Tremor	Other motor skills	Symptoms/ diagnosis
Seeber A et al. Int.Arch. Occup.Environ.Health. 2009	29/101/83	Styrene (Boat b)	6.4/ 5.8/ 6.3			-	-		+		-	+	-	(+)	-
Nilsson et al. Neurotoxicol. Teratol. 2010;	12/19	Toluene Printers (Previous)	34.8	-	-	(+)	-	+	-	-					(+)
Godderis L et al. Neurotox Res 2010 A: Exposed workers	144/ 53	Mixed S/ Chloroforme	4.9			-	+				+			-	
Dick FD et al. Occup Environ Med 2010[c]	124 /212	Mixed Solvents	5.1+ 1.9			+		-		+					
Number of epidemiological studies of exposed workers with +/ / -				4+ 10-	6+ 7-	13+ 2(+) 12-	5+ 1(+) 13-	5+ 1(+) 9-	10+ 2(+) 9-	5+ 1(+) 3-	11+ 1(+) 9-	8+ 7-	1(+) 1-	5+ 2(+) 5-	11+ 2(+) 5-
Epidemiological patient studies[d]															
Ellingsen DG et al. Int.J.Occup.Environ.Health. 1997	42/-	Mixed Solvents	22.5/10.0*	-	-	-	+			+		-			
Österberg K et al. Am J Ind Med.2000	26+31 /57	Mixed Solvents	>5/ CEI	-	+	+		+			+	+			+
Akila R et al. J Clin Exp Neuropsychology, 2006	11/11	Mixed Solvents	12.2				+		+						
Bast-Pettersen R Neurotoxicology 2009	48/144	Mixed Solvents	21.0			+	+		-	+		+			+
Godderis L et al. Neurotox Res 2010 B: CSE-Patients	33/ 53	Mixed Solvents	23.8			+	+				+			+	
*Number of epidemiological patient studies with +/ / -				0+ /2-	1+ /1-	3+ /1-	4+ /0-	1+ /0-	1+ /1-	2+ /0-	2+ /0-	2+ /1-	- /0-	1+ /0-	2+ /0-

Differences between groups in neuropsychological performance/or differences related to exposure parameters: Large/Statistically different: Red; p <0.05+; Tendency/Near significant: (Blue); p 0.05 -0.10 (+); No difference: Green. p >0.10 -; # The exposed subjects performed better, therefore the significant difference is counted as "-"

Type of exposure characterization: Duration of exposure (calculated as hours in some studies, but categorized as Year: Y;
CEI: Cumulative Exposure Index; Usually based on work history; job titles, years of employment.
OEL: Occupational Exposure Limit (Years);
The exposure is calculated in relation to the Occupational Exposure Limits.

Notes

a. Iregren A. Neurobehav. Toxicol.Teratol. 1982 also contains a group of spray painters exposed to mixed solvent. However, their results were also presented in Elofsson SA et al. Scand J Work Envir Health 1980, and therefore, only the results of the toluene group (rotogravure printers) are presented here.

b. Viaene MK et al. Occup.Environ.Med. 2001 divides exposed groups into one group for currently exposed N=27, and one group for formerly exposed N=90

c. Dick FD et al. Occup Environ Med 2010 This is a study of previously low-dose exposed subjects.

d. As the patients were all symptomatic, the categorization "symptoms" for the patients indicates that a specific symptom questionnaire was also applied

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4.7 Hydrogen sulphide

Hydrogen Sulphide (H_2S) is a common exposure in sewage and wastewater treatment plants, in oil and gas refineries, pulp and paper mill industries, farming, fishing industries, and generally in any place where bacterial processes involved in the decay of plant and animal protein take place. H_2S may also occur in outdoor environments, in sulphur springs, wetlands, and swamps, and wherever organic compounds containing sulphur undergo decay in anaerobic conditions (Guidotti 1996). It is a colourless gas that smells like rotten eggs in low concentrations (above 0.13 ppm), but which compromises or paralyzes the sense of smell at concentrations above 100 ppm (Svendsen 2001). The gas is easily flammable and explosive when occurring in higher concentrations in air.

Hydrogen Sulphide is not particularly soluble in water, and since water-solubility is critical in determining how deeply a gas penetrates the lungs, H_2S efficiently passes through the respiratory tract, is absorbed via the pulmonary blood supply, and is then distributed throughout the body (Klaassen et al. 1996). It interferes with the capacity of the blood's haemoglobin to transport oxygen to the body cells, and more directly with the capacity of cells to utilize intracellular oxygen in energy production (cellular hypoxia) (Birgersson et al. 1987).

Over the last decades, H_2S has been described in the literature as a nervous system gasotransmitter, necessary for optimal nervous system function (Kimura 2010 2015; Nagpure et al. 2015), contributing to the regulation of blood pressure and inflammation, and playing a possible protective role in neurodegenerative and cerebral ischemic disease (Reed et al. 2014).

H_2S is a well-known neurotoxic substance, and when entering areas where it exists at higher concentrations (> 500 ppm), exposure may lead to sudden spells of unconsciousness, or "knockdowns". Sudden releases of unpredictably high concentrations in specific work situations may also immediately cause such "knockdowns". Accordingly, an additional mechanism of injury is hypoxia due to reduced "access" to oxygen in breathing air for periods of time, and body tissue requiring regular oxygen supply, i.e., the CNS, will be particularly susceptible to injury (Guidotti 2010).

Repeated exposure to lower concentrations of H_2S (5–10 ppm) also seems to have resulted in chronic subjective nervous system symptoms such as fatigue, headache, poor memory, and concentration difficulty (Tvedt et al. 1991). The nature and course of symptom development, and the outcome of H_2S-exposure, whether stemming from acute or longer-duration exposure, is described in an extensive literature of case studies and patient groups. Some case reports describe transient improvement, and consecutive worsening of symptoms, followed by slow progress thereafter (Tvedt et al. 1991).

Occupational exposure

When present in confined spaces such as rooms or tanks, H_2S may displace breathing air closer to the ground or floor as it has a higher density, and is thus a little heavier, than air (Rumbeiha et al. 2016). At single exposure, levels above 1000 ppm H_2S may cause respiratory arrest and death (Svendsen 2001). In fact, H_2S is the second most common cause of fatal gas inhalation exposures at work after CO (Guidotti 2010). Identifying and measuring critical aspects of H_2S-exposure is challenging due to the unpredictable and sudden nature of peak exposure episodes. Peaks, concentration, and duration of exposure may all be of importance for determining the severity of a health hazard. The various possible injury mechanisms, i.e. via haemoglobin, intracellular, and hypoxia in confined spaces, in addition to a possible facilitating function of endogenously generated, or maybe even very low dose H_2S-exposure, complicate unified dose-response estimations for H_2S-toxicity. In occupational settings, H_2S will most often occur with co-exposures which also have potentially negative health effects (i.e. endotoxins/bacteria, CS_2), further complicating any attempt at determining an isolated dose-effect relationship for H_2S, based on occupational studies alone.

The short-term limit/excursion limit (STEL) is set to prevent acute toxic effects such as eye irritation, unconsciousness, and persistent neurological disorders (SCOEL 2007). Moreover, it is strongly advised that all exposure to rapidly rising high peaks of concentration be avoided

The occupational exposure limit values for hydrogen sulphide are 5 ppm (7 mg/m^3) as an 8-hour TWA and a short-term limits/ excursion limits (STEL) of 10 ppm (14 mg/m^3) (Arbetsmiljöverkets författningssamlingSwedish Work Environment Authority, (AFS)

Neuropsychological effects following H_2S exposure

In this review of neuropsychological H_2S-related group-studies, 348 papers in all were listed in the initial search. 166 papers did not cover H_2S and were excluded. 11 papers were review papers or could serve as background information for health effects due to H_2S-exposure, and 24 studies were selected for further evaluation for possible inclusion in the final literature review. Of these, N=15 were case studies or small series of cases. Only N=9 papers/studies, listed in table 7 *, met the ultimate inclusion criteria.

Neuropsychological testing has been used to assess and quantify cognitive or sensory/motor problems after occupational exposure to H_2S, and at lower exposure levels in the general public. We identified only two occupational group studies (De Fruyt et al. 1998; Farahat and Kishk 2010) covering nervous system effects and applying neuropsychological methods, both taking exposure as their criterium for inclusion. The occupational studies both involved possible coexposures, i.e., to endotoxins or CS_2.

Accordingly, we also included an experimental H_2S-study (Fiedler et al. 2008), in which healthy volunteers were exposed to controlled low-dose H_2S, without exposure peaks or coexposures.

The community studies (Inserra et al. 2004; Reed et al. 2014) were included because possible health effects from low-dose H_2S-exposure has been an issue of concern among sewage plant and wastewater workers. Such studies may, if purely exposure-based, at best illuminate both negative and possible positive/facilitating effects from ambient low-level H_2S exposure without unconsciousness. Still, the studies are subject to bias due to voluntary inclusion, despite exposure-based inclusion of participants. Neither Inserra et al. (2004) nor Fiedler et al. (2008) found any adverse neurobehavioral effects attributable to H_2S-exposure in an exposed neighbourhood, or in an exposure chamber, respectively. On the contrary, Fiedler observed a slight improvement in test performance in terms of speed/perceptual organization, manual motor dexterity, and sway/balance (Fiedler et al. 2008). In these studies, Digit Symbol, Fingertapping, Simple reaction time, SWAY test with eyes open or closed, and sensory function tend to be marginally better in the exposed groups compared to the controls. Some results in these studies may be in line with a hypothesis (in need of further study) that low-exposure H_2S might actually have facilitating effects on CNS-related performance (Reed et al. 2014), at least when it comes to short-term exposure in the exposure range 0.5–5 ppm (Fiedler et al. 2008), 0–64 ppb (0–0.064 ppm) (Reed et al. 2014), or close to 0.09 ppm (Inserra et al. 2004).

The Kilburn studies (Kilburn 1997; 2003; Kilburn et al. 1995; 2010) are widely cited, despite the profound criticism they have received (Guidotti 2010), basically because of their highly questionable validity, which is due to symptom-based inclusion, the inclusion of participants involved in litigation processes, and the incorporation of acute reactions in the exposure assessments. Some studies (Kilburn 1997; 2003) applied duration of H_2S-exposure only, rather than H_2S-measurements, or very few (Kilburn et al. 2010) measurements, not giving sufficient consideration to the exposure patterns, including various levels of exposure peaks, or whether the patients were actually exposed to the measured exposure levels. In these studies, symptoms are generally elevated, but this can be attributed to neither H_2S-exposure nor coexposures (endotoxins, CS_2), because the study design includes only patients.

The case studies of Tvedt et al. (1991) consider the course or progress of symptoms after exposure episodes, and also contain reviews of relevant literature covering injury course and development. The many case studies and series of cases indicate that nervous system symptoms occur frequently after acute exposure episodes, and that such symptoms may prevail over time/years after exposure in certain conditions, i.e., prolonged exposure due to acute unconsciousness.

In summary, the question of whether nervous system effects persist after low doses of H_2S remains inconclusive also based on the few group studies identified and included in this review, due to their inherent shortcomings related to both the selection into the studies, where recruiting is based on manifest symptoms, on patient groups, or people involved in litigation processes as plaintiffs in lawsuits. The group studies, particularly the occupational-based studies, primarily apply cross-sectional study designs, some of them also including control/reference groups or exposure differentiation. We have not identified any prospective study designs among the group studies on H_2S-health effects.

Studies including symptom description and neuropsychological examinations have been summarized in some recent reviews (Lewis and Copley 2015; Lim et al. 2016). Results have been difficult to interpret, since the studies of health effects from occupational exposures are often case studies or primarily based on manifest self-reported symptoms (Kilburn 1997; 2003; Kilburn et al. 1995; 2010). Our findings are in line with Lewis and Copley (2015), which included all neuropsychological studies in our current search. This almost complete overlap of included neuropsychological studies confirms the representativeness of our 2019 search strategy. Our search strategy also included the experimental Fiedler-study (Fiedler et al. 2008).

Observations from different studies may indicate that particularly low concentrations of H_2S may have protective dose-dependent effects when it comes to CNS-degeneration, through various mechanisms, whether anti-inflammatory, antioxidant, or antiapoptotic (Zhang and Bian 2014; Kida and Ichinose 2015). Some epidemiological studies have indicated better neurobehavioral performance in H_2S-exposed groups (Lewis and Copley 2015; Lim et al. 2016).

It thus remains unresolved whether long-term exposure to low concentrations of H_2S, poses a risk of nervous system injury, whether apparent symptoms are primarily context-dependent, or whether and when low-dose H_2S-exposure may have protective effects on the CNS, in isolation or in combination with other substances in the work environment.

Conclusion

Numerous case studies provide information regarding the nature and course of serious H_2S-exposure injuries, in particular when unconsciousness followed by hypoxia is involved.

The question of nervous system effects following occupational exposure to long-term low doses of H_2S without exposure peaks remains unresolved, considering that the few existing group studies have obvious shortcomings related to selection, exposure characterisation, and study design. Prospective low dose studies are lacking.

The community studies of low-dose ambient H_2S-exposure and experimental study designs are interesting in that context, as neuropsychological test profiles show that some tests results are marginally better among exposed than among control groups. In addition to methodological explanations, the literature on H_2S as a CNS gasotransmitter may be of value in understanding these observations.

Primarily, the unpredictable nature of H_2S-exposure in occupational contexts, along with its acute toxic and potentially fatal consequences, strongly imply that it is crucial that we minimize and prevent occupational exposure to H_2S.

This current overview can be considered complementary to the recent review by Lewis and Copley (2015). They also include studies reporting nervous system symptoms only, and have not limited their investigation to neuropsychological studies. On the other hand, this overview penetrates deeper into the neuropsychological test results.

*Compared to tables for other substances, a "Tremor"-column was deleted, as no studies included Tremor testing in the test batteries. "Other motor skills" refers to the SWAY-test and Grip strength. In addition, Kilburn (Kilburn et al. 1995; 2010; Kilburn, 1997) measures Blink Reflex that are not affected by H_2S in his studies. A "Sensory function"-column has been added, referring to Lanthony D15 Desaturated Color vision test, Perimetric Visual field testing, Visual acuity, Hearing tests, Auditory Evoked Response, and Vibro-tactile Threshold Tests applied in several of the studies. The "Symptoms"-column refers to symptom inventories made for the purpose of the study, or POMS – Profile Of Mood Scale.

Table 7. Neuropsychological effects in humans exposed to hydrogen sulphide (H_2S).

Epidemiological studies of exposed workers	N Expo/ referents	Type of exposure characterization	Years exposed	Verbal/ academic skills	Spatial skills/ perceptual organization	Speed information processing	Attention/ working memory	Verbal memory	Visual memory	Executive functions	Reaction time	Manual dexterity/ speed	Tremor	Other motor skills	Symptoms
Kilburn KH, Warshaw RH. Toxicol Indust Health 1995[a]	(22+13)/32 22 neighbours 13 workers	Y; A(s)(a); C; E(m) Outdoor H_2S: 0.01–0.1ppm Workers: 0.0–8.8 ppm	> 5 years	-	-	+	-	+	+	+	+	(+)	+	+	+
Kilburn KH. South Med J 1997[b]	16/353	Y; A(pr & sa); O; C; E(m) Minute-group: 328–10.000 ppm Peak. Hours-group: 1–50 ppm Years-group: 11–22 years	N=5: minutes N=6: 1–24 h N=5: 11–22yrs	+	+	+	+	+		+	+	+	+	+	+
De Fruyt F, et al. Int J Occup Environ Health. 1998[c]	(66+54)/67	A(s,p)(a,r); E(m);	>1 year		+	-	-	-	-			+	+		
Kilburn KH. South Med J 2003[d]	19/202	Y;C;	20min – 9 yrs	+	+	+		+		+	+	+	+	+	+
Inserra SG, et al. Environ Res 2004[e]	171/164	Y; A(s)(r); >0.09ppm H_2S estimate	>2yrs recidency	-		-	#-	+			-	+		#-	-
Fiedler N, et al. Environ Health Perspect 2008[f]	74 x 3 sessions	Y;A(s)(r); E(h) 0.05, 0.5, 5 ppm H_2S	2 hr x 3			#-		+			+	#-	#-	-	-
Farahat SA, Kishk NA Toxicol Indust Health 2010[g]	33/30	Y;A(s)(a);U;C; E(m)	>5yr sewer work. Mean 17.9 (6.68) yrs Range 5–27	+		+	+	+	+	+	+			+	+

Group differences in neuropsychological performance/or differences related to exposure parameters: Large/Statistical different: Red; p <0.05+; Tendency/Near significant: (Blue); p 0.05 -0.10 (+); No difference: Green. p >0.10 -; # indicate better performance in the exposed compared to control groups.
Exposure characterization: Duration of exposure (calculated as hours in some studies but categorized as Year: Y; Environmental sampling Air: A; Stationary (s) or personal (p) measurement strategy. Time weighted average (a) or Real time (r) monitoring, including peak exposures. Biological exposure indications: Urine: U. Health endpoint-based exposure indications: Smell/olfactory (O). Unconsciousness/symptoms (C). Exposure specificity (E): Primarily H_2S (h); Co-exposures (m), i.e. CS_2, VOC, Endotoxins, bacteria.

(continuation) **Table 7. Neuropsychological effects in humans exposed to hydrogen sulphide (H_2S).**

Epidemiological studies of exposed workers	N Expo/ referents	Type of exposure characterization	Years exposed	Verbal/ academic skills	Spatial skills/ perceptual organization	Speed information processing	Attention/ working memory	Verbal memory	Visual memory	Executive functions	Reaction time	Manual dexterity/ speed	Tremor	Other motor skills	Symptoms
Kilburn KH, Thrasher JD, Gray MR. Toxicol Indust Health 2010[h]	49 (26+23)/42	Y;A;O;C; Wastewater-employed: 2–74ppm H_2S, one 480 ppm exposure peak	Community participants: >4 yr recidency Wastewater-employed: Range 4–24 yrs employment.	+	+	+		+		+	+	+	+	-	+
Reed BR, et al. Neurotoxicol Teratol 2014[i]	1637 adults Male: N=656 Female: N=981 18–65 years	Y;A(s)(a);E(h) Ambient H_2S Four sub-groups: Q1: 0–10ppb Q2: 11–20ppb Q3: 21–30ppb Q4: 31–64ppb	Community participants: >3 yr recidency	-		#-	-	#-	-		#-	-			-
Number of studies with +/-				4 + 3 -	4 + 1 -	5 + 4 - 2 #	1 + 4 - 1 #	7 + 2 - 1 #	2 + 2 -	5 +	6 + 2 -1 #	5 + 1 (+) 2 - 1 #	5 + 1 - 1 #	4 + 3 - 1 #	5 + 3 -

Group differences in neuropsychological performance/or differences related to exposure parameters: Large/Statistical different: Red; p <0.05+; Tendency/Near significant: (Blue); p 0.05 -0.10 (+); No difference: Green. p >0.10 -; # indicate better performance in the exposed compared to control groups.
Exposure characterization: Duration of exposure (calculated as hours in some studies but categorized as Year: Y; Environmental sampling Air: A; Stationary (s) or personal (p) measurement strategy. Time weighted average (a) or Real time (r) monitoring, including peak exposures. Biological exposure indications: Urine: U. Health endpoint-based exposure indications: Smell/olfactory (O). Unconsciousness/symptoms (C). Exposure specificity (E): Primarily H_2S (h); Co-exposures (m), i.e. CS_2, VOC, Endotoxins, bacteria.

Notes

a. Kilburn KH, Warshaw RH. 1995: Exposed subjects were plaintiffs and included due to manifest symptoms. Measurement are stationary, and average registrations: we don't know to what extent the participants were exposed to H_2S, whether in terms of general exposure or peak exposure.

b. Kilburn KH. 1997: Subjects were referred patients, 12 of 16 were plaintiffs.

c. De Fruyt F. 1998: **Occupational study.** Subjects split into moderately (N=66) and highly (N=54) exposed, respectively. Combined CS_2 and H_2S exposure, effects from each could not be statistically disentangled. Inclusion of subjects based on >1-year exposure and exposure air sampling. The authors consider CS_2 the most important agent for toxic effects. Exposure was of little significance in explaining neuropsychological group differences.

d. Kilburn KH. 2003: Subjects were a case series of 19 patients, compared with controls, and 16 patients described in Kilburn KH (1997).

e. Inserra SG. 2004: Community-based study, exposure-based inclusion. Only "Match-to-sample" memory and Grip strength were marginally reduced. The marginal findings related to a Match to sample test and Hand Dynamometer do not relate to exposure status in a regression model.

f. Fiedler N. 2008: Experimental exposure study, three different exposure level conditions. The highest exposure (5ppm) relates to allowable exposure concentrations for workers expected to be exposed for 8 hr/day, 5 days/week, over a 40-year working lifetime. No peak exposures in this study.

g. Farahat SA & Kishk NA. 2010: The study is also published in Egyptian J Occup Med. 2009;33(2):253–70. **Occupational study,** exposure-based inclusion. 33 H_2S-exposed sewage network-workers with no history of unconsciousness. Mean H_2S exposure: 9.4 ppm inside manhole opening, 4.8ppm 0.5– 1 m away from opening. U-Thiosulfate as a H_2S exposure biomarker. Controls (N=30): Administrative staff matched for age, education, socioeconomic status.

h. Kilburn KH, Thrasher JD, Gray MR. 2010: **Community-based study.** Symptom-based inclusion and exposure estimation. Plaintiffs among the exposed group.

i. Reed BR, et al. 2014: **Community-based study,** exposure-based inclusion. Ambient H_2S exposure from geothermal sources 0–64 ppb, occasional 1000ppb (1ppm).

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5. Chemical substances' influence on neuropsychological domains

Attention/working memory, the ability to maintain information in temporary storage, usually from a few seconds up to a couple of minutes, can easily be measured through several tests involving relatively little effort. Several studies included tests for attention/working memory, but no clear tendency was observed. For the metals, roughly half of the studies reported at least one test result where this function was affected. However, there were more studies reporting problems with these functions among the CO studies. The same was found for the studies of patients with solvent induced encephalopathy.

Speed of information processing, the ability to perform simple repetitive cognitive tasks quickly and fluently, or in other words, the time it takes a person to perform a mental task. For most of the exposures, positive findings in this function outnumbered negative findings. While a meta-analysis of aluminium-exposed subjects by Meyer-Baron et al. (2007) found a significant effect on speed of information processing, this function was only significantly affected in 7 out of the 13 included aluminium studies in the present report. However, among subjects exposed to manganese, lead, and carbon monoxide, more studies reported this effect.

All in all, as speed of information processing is a function that is impacted by many diseases affecting the nervous system, a non-specific tendency to slower speed of information processing was found in several of the exposures in the present study.

Executive functions: This function was assessed in a limited number of studies. In the studies where it was applied, positive result findings seemed to outnumber negative findings, with one exception: this effect was not found for the mercury studies.

Spatial skills/perceptual organisation: An effect was reported in 10 out of 16 studies of lead, and in 8 out of 13 studies of mercury, while no effect was found for aluminium or manganese. Also, in the CO studies, the three studies including this function reported an effect. As this function is a central aspect of a person's intelligence, it is possible that a difference between groups regarding this function might indicate that the groups were not matched well in terms of intellectual function.

Verbal/academic skills. This central element in a person's general intelligence is often tested as a way to ensure that the groups under study are well matched, and in many studies, an adjustment is made for this function. In the studies of aluminium and solvents, and to a certain degree lead, most studies were negative, while for the other exposures there were

about as many positive as negative findings. In the same way as for spatial skills/perceptual organization, this function is a central factor of a person's intelligence, and differences between groups regarding this function might indicate that the groups were not matched well in terms of intellectual function.

Verbal memory was assessed in a limited number of studies. The reason why so few studies used tests for verbal memory is probably that these tests tend to be time-consuming. In the studies of lead, the majority of studies were positive, while for aluminium and solvents more negative than positive findings were observed. For the other studies, no clear effect was found.

Visual memory. No clear effect was found in the studies of visual memory. For most studies, there were as many positive as negative findings, with a tendency towards more negative findings in the studies of mercury.

Reaction time. In the studies of mercury, eight out of eleven studies where reaction time was tested were negative. For the other exposures, there were about as many negative as positive findings.

Manual dexterity/manual speed. Tests for manual dexterity, like finger tapping tests and pegboard tests are easy to administer and language-independent, and such tests have been applied in a number of studies. For three of the four metals–lead, manganese and mercury– impaired manual dexterity/manual speed where reported in a majority of the studies. This was not so for aluminium or solvents, where there was a tendency towards more negative findings.

Tremor. Tremor was reported in the majority of the studies of manganese and mercury. Only one study of lead included a tremor test, which yielded positive findings. Two out of seven studies of aluminium were positive, while the two solvent studies including tremor tests reported no effects on tremor.

Other Motor skills. As no specific term in the literature search covered "other motor skills" most studies included here were related to strength

or hand-eye coordination. In studies of manganese and lead, the positive studies outnumbered the negative ones, while no clear tendency was found for the other exposures. However, we have to make the reservation here that this category was used as a collective term, and is thus less specific than the other categories.

Symptoms/diagnosis of cognitive impairment. The Core Test Battery from the World Health Organization includes the (WHO NCTB) symptom questionnaire. In the studies where such a questionnaire was included the positive findings outnumbered the negative ones, with one exception (CO).

A symptom questionnaire is cheap and easy to apply. For this reason, one might expect that almost all studies would have included a symptom questionnaire, and many did. But, for instance, in the case of the epidemiological studies of solvents, 18 studies included a symptom questionnaire, while 27 studies included a test for speed of information processing and 21 studies included a test for visual memory or a test for reaction time.

6. Aspects of validity

The selection of studies

We used the previously mentioned criteria for inclusion: the study had to include at least one test that can be classified as a neuropsychological test, and the exposed group had to include > 10 subjects.

The exposed group had to be compared to either a control group, published norms, differences related to exposure parameters, or–in some studies–demographic "facts" such as diagnosis of dementia. Studies of subjects involved in litigation processes, were–with a few exceptions–excluded.

Other criteria for inclusion, such as response rate etc, were not applied. The present study represents more of a "State-of-the-art-review" than a "Critical review" (Grant and Booth, 2009). Therefore, if a study was published in a peer-reviewed journal, we accepted this as a implying a certain level of quality.

The choice of reference group(s)

In studies with control groups, the **choice** of control group is very important. Neuropsychological tests are not exclusively sensitive to brain pathology; performance in most of the tests is also strongly related to age and education, and for some tests, there are also gender-dependent differences (Heaton et al. 2004). Small differences in factors not related to exposure may therefore result in "findings" caused by differences between the groups under study. One of the most frequent problems when choosing a control group is finding groups that are similar in levels of education, occupation, or socioeconomic situation. Even small differences in cognitive capacities can have large effects on the outcomes. If the subjects in the control group have longer education and perform better on tests for intellectual function than the exposed subjects, this will increase the probability that the exposed subjects will be misclassified as having an impaired function.

Similar misclassifications can occur if the groups differ in terms of age. As several cognitive functions deteriorate with increasing age, age-matching is important.

The use of published norms as a substitute for a reference group

The use of published norms can lead to similar problems as the use of an inappropriate reference group. Heaton et al. (2004) showed that if the norms are not specific with regard to age and education, then the sensitivity of the tests–the ability to detect injuries–will be best when the subjects are elderly or less educated. On the other hand, the specificity will be lower for older or less educated subjects. They will more often be classified as "brain

damaged" despite being healthy. The opposite applies to younger and well-educated subjects. They can be misclassified as "normal" i.e. as not having a cerebral impairment even when they have been diagnosed as brain-damaged (Heaton et al. 1991). Gade et al. (1988), illustrated this problem when they reanalysed the test results for a group of CSE patients who had been diagnosed on the basis of comparisons with published norms. When the patients were compared with referents instead of with published norms, the evidence of impairment disappeared (Gade et al. 1988).

Suboptimal performance and motivational aspects of the neuropsychological examination

A neuropsychological examination is based on the assumption that the patient does his best. A patient being tested to assess whether, for instance, he will be permitted to keep his driver's licence will be highly motivated to perform at his best. However, when the neuropsychological examination is made in connection with a claim for financial compensation, the patient may fear that good test results could harm their chances of being awarded payment (Bast-Pettersen 2008).

The role of motivational aspects has been associated with the concept of cognitive malingering (Greve et al. 2006), or suboptimal performance (van Hout et al. 2003). Malingering can be defined as the intentional exaggeration or fabrication of illness or disability motivated by external incentive. Greve et al. (2006) estimated that indications of malingered cognitive dysfunction were found in from 30% to over 45% of subjects with an identifiable financial incentive. van Hout et al. (2003) reported that 46% of a group of solvent-exposed patients failed one of two tests for malingering, though only 18.6 % failed both tests.

Ways of categorising tests

There are several ways to categorize tests. While it is quite obvious what some of the tests measure, this is not so for many others.

Some tests can be classified as tests for **Memory,** but also as tests for attention/working memory. An example of this is the WAIS subtests Digit Span, which was often categorized as memory in older literature, but which we categorise as attention/working memory in the present study. The Digit Span Backwards is also in some studies classified as executive functioning.

More complicated is the use of the term **Executive Function,** which is supposed to test frontal lobe function and cover such aspects as decision making, following and adjusting plans, and distractibility. As previously mentioned, central aspects are volition, planning, purposive action and effective performance (Strauss et al. 2006). Some tests are regarded as "typical" tests of this function, like the Wisconsin Card Sorting Test (Strauss et al. 2006). The Stroop Color/Word is another example of a test meant to measure executive function. However, when designing large

studies of exposed subjects, these tests are often not the ones chosen, mainly due to the time available. Often, the Trail Making Test B is chosen as a measure of this function. In the present study we categorized the Trail Making B as a test of executive function. This is in accordance with the classification used in the Professional Manual for norms for an expanded Halstead-Reitan Battery (Heaton et al. 2004) and in accordance with several other studies in the field of neurotoxicology, for instance the study by Meyer-Baron et al. (2013). Other studies have categorized the Trail Making B as a test of ”cognitive speed, visual scanning” (Bast-Pettersen et al. 2004) or as a test for ”attention/processing speed” (Van Valen et al. 2012), or ”complex attention” (Van Valen et al. 2018).

In a study of the Stroop test, the Stroop test was compared with other tests, including the Trail Making Test B (Bast-Pettersen 2006). The correlation between Stroop Color-Word and Trail Making B was quite high (0.62), indicating that 38 percent of the variance was common for the two tests. This is an indication that these two tests to a large degree measure the same type of function. However, the correlation was also high between Stroop Color-Word and WAIS Digit Symbol (0.61) and between Stroop Color-Word and the Trail Making Test A (0.55). The highest correlation (0.71) was observed between the Trail Making Test B and the WAIS Digit Symbol, a test categorized as a test for Speed of information processing. The difference between tests for speed of information processing and executive functions is probably not as clear as their division into separate categories may suggest.

Categorising the Trail Making Test B as a test for executive function can give the impression that the study has a higher quality and have applied more advanced neuropsychological methods than it actually does.

Another problem is the **assessment of tremor.** While the accelerometers like the CATSYS TREMOR pen are definite tremor tests, the Kløve-Mathews Static Steadiness Test/Nine Hole Steadiness Test is something of a cross between a tremor test and a test for hand-eye coordination (Bast-Pettersen and Ellingsen 2005). Other tests, like the Eurythmokinesimeter (EKM) (Wastensson et al. 2008) which measures precision (Eye-hand-coordination) and tempo, are in the present study categorised as **Other Motor Skills.**

As it is important for the groups under study to be similar in terms of cognitive functions, the function **Verbal Academic Skills** is often used as a way of ensuring that the groups will be similar enough. But should an exposure lead to impairment in this function, there is a danger that it will go undiscovered, for example if the comparisons between exposed and unexposed groups are adjusted for level of Verbal Academic Skills along with age etc.

Choice of test methods

When planning an epidemiological study, the selection of tests is important, as you cannot find that which you have not examined. It can be argued that in non-positive studies, the researchers failed to find a difference between groups due to a non-optimal selection of tests. This may be the case for some non-positive studies, but as it is in the interest of most researchers to disclose possible effects, they will therefore tend to select tests that are known to be sensitive enough to detect even small effects.

Symptom questionnaires

In some studies, the category **Symptoms/diagnosis** refers to demographic "facts" such as a diagnosis of dementia. However, in the studies where a diagnosis (for instance Alzheimer's disease) was the endpoint, only studies involving neuropsychological tests were included.

As the present study is a study of neuropsychological functions, the decision to exclude studies in which symptom questionnaires were the only measure of cognitive function used was based on the fact that a symptom questionnaire is not a neuropsychological test.

Self-reported conceptions of cognitive abilities in occupational and environmental health settings can only be trusted to a limited degree. This was illustrated in a study where more than 400 men in manual occupations answered a neuropsychiatric questionnaire (the Q 16) before being tested with a neuropsychological test battery (Bast-Pettersen 2006). With one exception, none of the questions related to memory function were predictive of memory test results. None of the memory tests showed weaker results for participants answering "Yes" to the simple memory question "Do you have a short memory?" or the question "Have your relatives told you that you have a short memory?" (Bast-Pettersen 2006). However, a question about concentration problems predicted, to a certain degree, performance on tests for attention, speed, and reaction time. (Bast-Pettersen 2006).

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7 Preventive aspects

In general, the **use** of certain neurotoxic substances such as inorganic mercury, lead and solvents has decreased sharply or almost ceased in Swedish work environments, and has been replaced by the use of less toxic substances. Moreover, **exposure levels** have decreased substantially due to better working conditions (Sällsten et al. 1990; Bast-Pettersen 2009).

Still, approximately 35,000 people work full-time as welders in Sweden, and welding is also included as one of several tasks for several other occupational groups. Welders represent the occupational group that has the most exposure to manganese (Lucchini et al. 2015).

Moreover, with an emerging and ongoing societal transformation towards a more ecologically sustainable economy that emphasises recycling, occupational exposure to substances like H_2S may become increasingly common in industries related to such activities in years to come. Workers involved in the collection, transportation, and recycling of EEE-waste may be exposed to neurotoxic metals such as lead and inorganic Hg (Julander et al. 2014).

Systematic work environment management refers to employers' efforts to regularly investigate, carry out, and follow up activities in such a way that health concerns and accidents are prevented, and a satisfactory working environment is achieved (Swedish Work Environment Authority's Statue Book (AFS): 2001:1).

The central activities are:

- examination of the organisation
- assessment of the risks revealed by this examination
- measures to reduce such risks
- verifying that the measures taken have contributed to a better work environment

Risk assessment

When dealing with chemical risks, special methods of risk analysis are often necessary. The first step is to consider whether these risks could be eliminated or reduced "at the source". If a risk cannot be avoided completely, it is important that the employees be protected in other ways, for example through education, support and guidance, or personal protective equipment.

Risk assessment should always result in the proposal of measures for eliminating or reducing the risks. Occupational-hygienic and other

measurements may be needed as part of the risk assessment process. **Occupational health services** may provide vital support when competence is insufficient or lacking in the employer's own activities.

Information/education

The employer is obliged to ensure that workers have received sufficient instruction on the correct way to handle products containing neurotoxic substances, on the risks that exist, and how these risks are best avoided. Furthermore, the employer should provide workers with instructions on how to minimise the exposure and proper use of personal protection equipment. Additional written information such as safety data sheets should be readily available in the workplace.

Surveillance of exposure

Occupational exposure limit values are based on scientific documentation that comprises all adverse effects, including effects on the CNS, and are subject to revision in the face of new discoveries. Surveillance of the hygiene conditions at the workplace can be carried out by monitoring levels of aluminium, lead, manganese in dust, and inorganic mercury and various solvents in air, and comparing them to current hygienic limit values (Swedish Work Environment Authority; AFS 2018:1). No detectable effects on an individual basis are to be expected following exposure to these substances in normal working conditions, but subtle long-term effects on a group basis may occur even at exposure levels close to the hygienic limit value. For this reason, it is essential that exposure levels from these potential neurotoxic substances be kept as low as possible.

Short-term high exposures to certain substances (i.e., H_2S and CO) may cause very serious effects. Exposure to higher concentrations (> 500 ppm) of H_2S may lead to sudden unconsciousness upon entering such areas. Identifying the risk and acting, for example avoiding sole work, is the first step. Measurement equipment at fixed locations may indicate general exposure levels, such as 8-hour time-weighted average (TWA), but need not necessarily catch peak exposures of short duration or the accumulated exposure burdens of different individuals. Real-time personalised measurement equipment carried by workers may identify both individual low-level exposure and peak exposures. Refined job-exposure matrixes (JEM) with individualized exposure indexes combining concentration, exposure peaks, duration, and work tasks may also be informative (Austigard et al. 2018).

Personal protective equipment

Use of personal protective equipment may reduce exposure substantially (Keer et al. 2018). The main exposure route for most of these substances

is inhalation, but dermal exposure may also be important. The employers are obliged to inform the employees about the kinds of hazards that their personal protective equipment is intended to protect against (Swedish Work Environment Authority, AFS 2001:3).

Biological monitoring

Biological monitoring of workers enables surveying of exposure on an individual basis. The concentration of lead in blood (B-Pb) is the most commonly used biomarker for lead exposure. Blood samples are useful for detecting short-term exposure to inorganic mercury at higher levels, while urine samples are considered the best indicator of body burden due to long-term exposure (WHO, 2003). Workers exposed to lead and inorganic mercury are covered by a monitoring system that involves periodic biological exposure control of lead and inorganic mercury concentration in blood, and regulations that require them to discontinue work at high blood levels. (Swedish Work Environment Authority, AFS 2019:3).

Medical checks

As previously mentioned, workers exposed to lead and inorganic mercury are covered by a monitoring system, and it also involves periodic medical examinations. Its main purpose is to identify individuals with diseases that make them particularly sensitive to and conditions that could be exacerbated by exposure. Moreover, in connection these medical visits, the physician may inform them about risks and offer advice on how to minimise exposure, e.g., careful hand hygiene to avoid hand-to-mouth transmission of lead in connection with snuff and food intake.

Pregnant or nursing women

Pregnant or nursing women may not be employed to work with lead according to the Swedish Work Environment Authority's statutory collection "Pregnant and Nursing Workers," (Swedish Work Environment Authority, AFS 2007:5). A risk assessment must always be performed when pregnant or nursing women are at risk of being exposed to any type of neurotoxic substances.

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