Chlorinated Solvents

Health effects after long-term exposure. Public Health Perspectives.

Rasmussen, Kurt

Publication date:
1997

Chlorinated Solvents

Health effects after long-term exposure.

Public Health Perspectives.

Kurt Rasmussen

Institute of Epidemiology
and Social Medicine
University of Århus

Department of Occupational Medicine
Herning Hospital

Contents **Page**

Suppl. I: Rasmussen K, Sabroe S. Neuropsychological symptoms among metal workers exposed to halogenated hydrocarbons. Scand J Soc Med 1986;14:161-8.

Suppl. II: Rasmussen K, Jeppesen HJ, Sabroe S. Solvent-induced chronic toxic encephalopathy. Am J Ind Med 1993;23:779-92.

Suppl. III: Rasmussen K, Jeppesen HJ, Sabroe S. Psychometric tests in assessment of brain function after solvent exposure. Am J Ind Med. 1993;24:553-565.

Suppl. IV: Rasmussen K, Sabroe S, Arlien-Søborg P. Clinical neurological findings among metal degreasers exposed to chlorinated solvents. Acta Neurol Scand 1993;87:200-4.

Suppl. V: Rasmussen K, Brogren CH, Sabroe S. Subclinical affection of liver and kidney function by solvent exposure. Int Arch Occup Environ Health 1993;64:445-8.

Suppl. VI: Rasmussen K, Sabroe S, Wohlert M, Ingerslev HJ, Kappel B, Nielsen J. A genotoxic study of metal workers exposed to thrichloroethylene. Sperm parameters and chromosome aberrations in lymphocytes. Int Arch Occup Environ Health 1988;60:419-23.

Suppl. VII: Christensen JM, Rasmussen K. Danske arbejderes udsættelse for triklorethylen 1947-87. Ugeskr Læger 1990;152:464-7.

0.0. Preface and Acknowledgements

This Ph.D. thesis consists of an overview of the toxicity of chlorinated solvents and a review of the history of solvent syndrome, as well as seven previously published articles. The work contained here was started while I was employed at the Institute of Epidemiology and Social Medicine, University of Aarhus, and completed at the departments of occupational medicine in Aarhus and Herning.

It was Anders Bjerre Mikkelsen who first drew attention to chlorinated solvents, singling them out as a particularly interesting sub-category of organic solvents. In 1980, when Anders Bjerre Mikkelsen was a lecturer at the Institute of Chemistry, University of Aarhus, he initiated contacts with physicians occupied with social medicine in the Aarhus area with an interest in occupational medicine. A work group was established and in 1983 we wrote a book titled "Chlorinated Solvents - A work Environment Problem", which was published by Fremad. This comprised a quite thorough review of the literature concerning toxicology and work environment conditions related to exposure to chlorinated solvents. Work on this book gave rise to discussions concerning the lack of knowledge about chlorinated solvents and to the ideas leading to the studies that are described in the overview part of this thesis.

I would like to give special thanks to Svend Sabroe, physician and lecturer at the Institute of Epidemiology and Social Medicine, University of Aarhus, for his continual willingness to provide supervision and for his collaboration and much valued friendship. The planning and execution of the clinical study were aided by a fruitful collaboration with psychologist Hans Jeppe Jeppesen. I have relied heavily on the help of a number of secretaries through the years: Hanne Kærgaard, Annelise Witt, Kirsten Bendixen and Nora Jakobsen - thanks for your wholehearted efforts.

I would also like to thank those who have supported this research financially: Sygekassernes Helsefond and The Danish Medical Research Council.

Aarhus september 1996 Kurt Rasmussen

1.0. English summary

The primary critical effect of occupational exposure to organic solvents is the neurotoxic effect and risk of brain damage; chronic, diffuse cerebral injury. For a long time however, chlorinated solvents have been associated with a broader range of toxic effects. Since the industrial introduction of chlorinated solvents in the beginning of this century, symptoms relating to cranial and peripheral nerves have been identified. During the last few decades, toxic effects on the liver and kidneys, cardiac effects and mutagenic outcomes have also been recognised. The purpose of the present study has been to examine the risk of developing a broad range of health injuries amongst workers occupied with metal degreasing, a group whose exposure risks are relatively restricted to chlorinated solvents, trichloroethylene (TRI) being the dominant example.

Out of 283 metal working companies in the county of Aarhus, 72 used solvents for metal degreasing and cleaning. The 240 workers employed by these companies constituted the primary study sample, who, along with a control group of 350 non-skilled metal workers, participated in a preliminary questionnaire study. This was used to identify those who used TRI or fluorocarbon 113 as degreasing agents, for the purpose of undergoing a detailed program of clinical examination. 99 out of a possible 116 chose to participate. A cohort study was chosen as the research design, with a single follow-up after 2½ years. The analysis strategy has primarily involved dose-response analyses in a study sample with cumulative exposures varying between 1 month and 36 years. An index for cumulative solvent exposure was calculated on the basis of occupational history, and three exposure groups were formed with total no. of years with full-time exposure distributed as follows: 0.5 (0.05-0.9) years, 2.1 (0.91-3.8) years, and 11.0 (4.0-35.6) years. Supplementary information was obtained in the form of historical exposure data from The Working Environment Service, who had undertaken 1544 biomonitoring measurements of urinary TRI-metabolites amongst metal degreasers in companies from the whole of Denmark between 1947-87. From this material it appears probable that metal degreasers from the mid-1950's to the mid-1970's have been exposed to levels of TRI equivalent to 2/3 the allowed limit of 30ppm. A third set of exposure data consists of measurements of the present level of TRI-metabolites, taken from both blood and urine, and is used primarily to control for on-going exposure.

A diagnosis of organic psychosyndrome was given on the basis of neurotoxicological symptoms,

clinically demented behaviour, and, as the decisive factor, performance on psychometric tests, that were adjusted for the effects of age, the level of primary intellectual functioning, and word-blindness. The prevalence of "mild" or "mild to moderate" organic psychosyndrome was found to be 10.5% in the low exposure group, 38.9% in the medium exposure group, and 63.4% in the high exposure group. The risk of developing organic psychosyndrome was proportional to exposure duration, increasing age and decreasing primary intellectual level. Using logistic regression analysis, in which the effects of 6 potential confounders were controlled for, it was found that there is an increased risk of developing organic psychosyndrome following long-term solvent exposure. The odds ratio for the medium exposure group was 5.6 (0.93-34.3), and for the high exposure group 11.2 (1.9-66.6), being significant in the last group only.

It is recognised that psychometric tests play a key diagnostic role in neurotoxicological studies, but which test elements are the most sensitive for the neuropsychological evaluation of solvent exposed workers, and what role does confounding play? In a test battery of 15 tests and 29 sub-tests, we found the strongest associations with solvent exposure with tests of attention: audio-motoric functioning and PASAT, as well as the visual gestalts of the learning and memory tests. The main confounders were primary intellectual functioning, age and education.

The neurological examination was able to demonstrate a significant dose-response relationship between cumulative solvent exposure and motoric dyscoordination, a relationship that remained after controlling for confounds. On the other hand, a bivariate association between solvent exposure and the threshold for vibration sensitivity, measured as an expression of peripheral neuropathy, disappeared after multivariate control, in which age and signs of arteriosclerosis were the dominant confounders. Cranial nerve outcomes, that are reported in the literature as being associated with TRI exposure, were found in the form of affected sensory functioning of n. trigeminus, n. facialis and n. olfactorius, with a low prevalence and weak dose-response relationship.

Liver functioning was tested with 6 parameters and kidney functioning with a nephrotubular enzyme. We found a trend toward a dose-response relationship between long-term exposure to TRI and the liver function test, gamma-glutamyltransfase, as well as the renal tubular enzyme N-acetyl-beta-glycosaminidase, though the association was weak and became non-significant after controlling for confounders.

Genotoxic examination was carried out with 15 metal degreasers with high TRI-exposure levels. A slight but non-significant increase was found of 2 fluorescent nuclei in sperm cells, indicators of the chemically induced presence of 2 Y-chromosomes. More notable was the finding of a highly significant increase in the frequency of unstable chromosome changes in cultivated lymphocytes: gaps, breaks, translocations, deletions and inversions. Both effect parameters were studied in relation to reference groups, there was however, no possibility for proper confounding analysis. The finding ought though to be considered as a warning signal regarding possible effects on the male reproduction system.

Thus, this study has demonstrated a broad profile of health related effects associated with long-term exposure to chlorinated solvents, primarily TRI. The level of exposure in this study sample is estimated to have been approximately 20 ppm from the 1960's and 20-25 years thereafter. This level of exposure is likely to be typical in many industrialised, as well as developing, countries. On the 1st January 1994, the allowable limit of TRI was lowered from 30 ppm to 10 ppm in Denmark. After years in which the consumption of TRI in Denmark has been falling, a renewed increase in its use may be expected, as a result of the prohibition of other chlorinated hydrocarbons. Relevant work hygiene measures need to be observed. In the case of metal degreasing with TRI, the following steps are necessary: The implementation of working routines that minimize TRI release, proper maintenance of TRI-vapour plants, use of respiratory protective equipment, and, as a means of health surveillance, a continuous monitoring of trichloroacetic acid in urine. The most effective preventive measure is substitution with non-solvent based degreasing agents such as alkaline soap solution.

This review contains a description of the study on chlorinated solvents which is placed within a larger perspective, and an overview of the history and present consumption patterns of chlorinated solvents. The sequence of events relating to solvent conditioned brain damage, from the earliest medical investigations to scientific and public recognition, is also reviewed. Finally, the importance of the debate on solvent syndrome for the regulation of exposure to organic solvents, and the general focus on occupational health and safety in Denmark during the last 15-20 years, is discussed.

2.0. Danish summary.

I relation til erhvervsmæssig udsættelse for organiske opløsningsmidler er den primære kritiske effekt den neurotoksiske effekt og risikoen for hjerneskade - en kronisk diffus cerebral skade. Klorerede opløsningsmidler har imidlertid længe været kendt for en mere bredspektret toksicitet. Siden den industrielle introduktion af klorerede opløsningsmidler i begyndelsen af dette århundrede har det drejet sig om udfald fra kranienerver og perifere nerver. De seneste årtier endvidere lever- og nyretoksicitet, cardial påvirkning samt mutagenicitet. Formålet med det aktuelle studie har været at undersøge risikoen for udvikling af en bred profil af helbredsskader blandt metalaffedtere, en gruppe, der er relativt monoeksponerede for klorerede opløsningsmidler med trichlorethylen (TRI) som det dominerende opløsningsmiddel.

Blandt 283 metalvirksomheder i Århus Amt brugte 72 virksomheder opløsningsmidler til metalaffedtning og rensning. De herved beskæftigede 240 arbejdere udgjorde den primære undersøgelsesgruppe, som sammen med en kontrolgruppe på 350 ufaglærte metalarbejdere deltog i en indledende spørgeskemaundersøgelse. Herfra valgtes alle, der affedtede med TRI eller fluorocarbon 113, som deltagere i et detaljeret klinisk undersøgelsesprogram, 99 ud af 116 mulige deltog. Studiedesignet er et kohortestudie med et enkelt follow-up efter 2½ år. Analyseideen har primært været dosisresponsanalyser i en studiegruppe med variation i akkumuleret eksponering fra 1 måned til 36 år. Et index for kummulativ opløsningsmiddeleksponering blev udregnet på basis af erhvervsanamnesen, og der blev etableret 3 eksponeringsgrupper med livslang fuldtidseksponering, fordelt som henholdsvis 0,5 (0,05-0,9) år, 2,1 (0,91-3,8) år og 11,0 (4,0-35,6) år. Der blev suppleret med en opgørelse af historiske eksponeringsdata fra Arbejdstilsynet, idet der fra perioden 1947-87 forelå 1544 biomonitoreringer af TRI-metabolitter i urinen hos metalaffedtere fra virksomheder spredt ud over Danmark. Det kan herudfra sandsynliggøres, at metalaffedtere fra midt i 50'erne til midt i 70'erne har været udsat for eksponeringsværdier på ca. 2/3 af grænseværdien på 30 ppm. Som et tredie sæt eksponeringsdata er det aktuelle niveau af TRI-metabolitter undersøgt i både blod og urin, primært som kontrol af pågående eksponering.

Diagnosen organisk psychosyndrom blev stillet på basis af neurotoksiske symptomer, klinisk dementiel adfærd samt som det afgørende præstationer i psykometriske tests, der blev søgt justeret for effekten af alder, primær intellektuelt funktionsniveau samt ordblindhed. Prævalensen af "let" eller "let til middelsvær" organisk psykosyndrom blev fundet til 10,5% i den

laveksponerede gruppe. 38,9% i den mellemeksponerede gruppe og 63,4% i den højeksponerede gruppe. Risikoen for at udvikle organisk psykosyndrom var proportional med varigheden af eksponering, stigende alder og faldende primær intellektuelt niveau. Efter logistisk regression med justering for effekten af 6 potentielle confounder variable blev der fundet en forøget risiko for udvikling af organisk psykosyndrom efter lang tids opløsningsmiddeleksponering. I den mellemeksponerede gruppe var odds ratioen lig 5,6 (0,93-34,3), i den høj-eksponerede gruppe 11,2 (1,9-66,6), d.v.s. kun signifikant i sidstnævnte.

Det er anerkendt, at psykometriske test har en diagnostisk nøglerolle i neurotoksikologiske studier, men hvilke testelementer er mest sensitive i neuropsykologisk vurdering af opløsnings-middeleksponerede arbejdere, og hvilken rolle spiller confounding? Vi fandt i et testbatteri på 15 test med 29 subtest den stærkeste association til opløsningsmiddeleksponering for opmærksomhedstestene akustisk-motorisk funktion og PASAT samt indlærings- og hukommel-sestesten visuelle gestalter. De dominerende confounders var primær intellektuel funktion, alder og uddannelse.

I den neurologiske undersøgelse blev der demonstreret en signifikant dosis respons sammenhæng mellem kummulativ opløsningsmiddeleksponering og motorisk dyskoordination - en relation som blev bibeholdt efter confounderkontrol. Derimod forsvandt en bivariat association mellem opløsningsmiddeleksponering og tærsklen for vibrationssans, målt som et udtryk for perifer neuropati, efter multivariat kontrol, hvor især alder og tegn på arteriosclerotisk sygdom var dominerende confounders. De fra litteraturen kendte kranienerveudfald efter TRI eksponering blev fundet som påvirket sensorisk funktion af n. Trigeminus, n. Facialis og n. Olfactorius, i lav prævalens med svag dosis respons relation.

Leverfunktionen blev testet via 6 leverfunktionsparametre og nyrefunktionen via et nefrotubulært enzym. Vi fandt en tendens til dosisrespons relation mellem langtidseksponering for TRI og levertesten gamma-glutamyltransferase samt nyretubulienzymet N-acetyl-betaglycosaminidase - en svag association, som blev insignifikant efter confounding kontrol.

Genotoksiske undersøgelser blev udført hos 15 affedtere, højeksponerede for TRI: Der blev fundet en lille, men insignifikant forøgelse af 2 fluorescerende kærner i sædceller som indikator for kemisk induceret tilstedeværelse af 2 Y-kromosomer. Mere markant blev der i dyrkede lymfocytter fundet en højsignifikant forøget hyppighed af ustabile kromosomforandringer: gaps, breaks, translokationer, deletioner og inversioner. Begge effektparametre blev studeret i forhold til referencegrupper, imidlertid var der ikke mulighed for egentlig confounderanalyse. Fundet må

dog opfattes som et faresignal om påvirkning af mandlig reproduktion.

Dette studie har således demonstreret en bred profil af helbredseffekter med sandsynlig relation til langtidsudsættelse for klorerede opløsningsmidler, primært TRI. Eksponeringsniveauet i dette studie antages at have ligget på omkring 20 ppm fra 1960'erne og 20-25 år frem. Sådanne eksponeringsniveauer er sandsynlige i såvel mange industrialiserede lande som udviklingslande. Fra 1. Juli 1994 er grænseværdien sænket fra 30 til 10 ppm i Danmark. Efter en årrække med faldende forbrug af TRI i Danmark er der pga forbud mod andre klorerede kulbrinter, påny stigende anvendelse af TRI. Relevante arbejdshygiejniske forholdsregler bør iagttages. Ved metalaffedtning med TRI: organisering af en arbejdsgang, der minimerer udslip af TRI-dampe til arbejdslokalet, vedligeholdelse af TRI-dampaffedtningsanlæg, brug af åndedrætsværn - og som helbredsovervågning, en løbende måling af trikoreddikesyre i urinen. Den mest effektive forebyggelse er substitution til ikke-opløsningsmiddelbaserede affedtningsmidler såsom alkalisk sæbevand.

Dette review indeholder ud over en gennemgang og perspektivering af undersøgelsen om de klorerede opløsningsmidler, en oversigt over klorerede opløsningsmidlers historie og aktuelle forbrugsmønster. Endvidere gennemgås forløbet vedrørende opløsningsmiddelbetinget hjerneskade fra de tidligste medicinske undersøgelser til videnskabelig og offentlig anerkendelse. Endelig beskrives den betydning debatten om opløsningsmidler har haft for regulering af eksponeringen af organiske opløsningsmidler og for det generelle danske focus på arbejdsmiljø gennem de sidste 15-20 år.

3.0. Background and aim.

Chlorinated hydrocarbon solvents made their appearance in industry and trade at the end of 18th century. Carbon tetrachloride was the first chlorinated solvent produced for industrial purposes. However, it became apparent that carbontetrachloride was a powerful acute hepatotoxic and nephrotoxic agent, and to decrease these health risks it was replaced by trichloroethylene (TRI) (162, VII). Since about 1910 TRI has been a dominant solvent for degreasing in the metal industry, such as for degreasing components prior to painting, anodizing and electroplating. Other fields of application are in drycleaning, as a solvent for organic products, and as a substance in adhesives.

Throughout the last decade, in some countries including Denmark, there has been a trend towards toxicologically-based substitution for TRI to products such as 1,1,1-trichloroethane and the halogenated product 1,1,2-trichloro-1,2,2-trifluoroethane (CFC 113). The consumption of TRI in Denmark has decreased from 4,000 tons/year in 1978 to around 1200 tons/year in 1994. Internationally, production and sales have been stable for some decades in the USA and Europe accounting for about 250,000 tons each per year and in Japan at about 70,000 tons/year (8). The number of daily or frequently exposed workers are estimated to be 5000 in Denmark and 3,5 mio in USA (34).

The acute, narcotic effects of solvents have been known for a long time and some of the industrial solvents have a history of use as general anaestetics, e.g. TRI. The critical effect of solvent exposure is, however, chronic central nervous system-toxicity. The subject of debate and controversy over two decades has been: does long-term exposure to solvents increase the risk of chronic irreversible brain dysfunction? The studies traditionally considered in favour of this hypothesis are four Scandinavian case-control and cohort studies from 1976-85 based on disability pension registers - with findings indicating consistent risk estimates of 2-3 of getting a neuropsychiatric disability pension after solvent exposure (12, 105, 118, 132). This register-based design has been reexamined in Holland and Switzerland with non-significant or low risk relationships between solvent exposure and dementia (75, 173). However, in a recent American study of the same design there was found a significant over-all odds ratio of 1,4 for chronic neuropsychiatric disabling conditions (29). The same discrepancy has been demonstrated in several clinical cross-sectional studies with positive outcome in studies from Scandinavia and

insignificant findings in most investigations from other countries (54, 86, 165, 177). However, a couple of newer American studies including clinical psychological examination give supportive evidence along with the Scandinavians (24, 113).
Among industrial solvents in present use TRI belongs to those which have been the concern of most neurological and occupational investigations since the beginning of this century, known for the ability to cause cranial nerve damage. Reports on a broad spectrum of neurotoxicity are, however, mostly based on case-studies, and accidental circumstances (60, 119). The neurological literature on TRI falls into three parts.

A few years after the introduction of TRI in the German machine and aeroplane industry in the beginning of this century, Plessner reported the first cases of trigeminal analgesia (134). The problem, with cranial nerve affection especially involving the Vth nerve, peaked with the use of TRI as a general anaesthetic about 1935. The effects were attributed to the contact of TRI with lime soda used as an adsorbant in anaesthetic apparatuses, resulting in the formation of the decomposition product: dichloroacethylene (8). After elimination of this factor a decline in side effects was observed. Still there have been current case histories on cranial nerve disturbances or fatal cases with severe histological alterations in the central nervous system after accidental overexposure or degreasing within confined spaces (59, 99).

The second part of these neurotoxicological studies concerning TRI has focused on neurobehavioral toxicity reporting, "neurosis" or "psychoorganic syndrome" among industrial cohorts. In this period so far, 10 studies on psychoorganic syndrome have been published (4, 19, 21, 55, 72, 93, 102, 107, 152, 167). However, these studies have been performed without proper control for confounding factors, beside the lack of diagnostic sufficiency as they are based on symptom registration. Only the 1955 Swiss study of metal degreasers by Grandjean stand out as a methodologically well-founded study giving support for the existence of chronic toxic encephalopathy associated to TRI-exposure (72).

In a third pool of these neurostudies originating from the last 15 years, the primary interest has been neurological and neurophysiological outcomes. The findings were insignificant affection of nerve conduction velocity or trigeminal somato-sensory evoked potential, the clinical relevance of which is questionable (20, 144).
Severe liver and kidney damage has been described related to circumstances of over- exposure

to TRI, i.e. sniffing or accidental occupational exposure (160). The liver seems to be more vulnerable than the kidney. However, evidence of the hepato- and nephrotoxic potential of halogenated hydrocarbons currently involves an unsolved problem (41, 46).

TRI has been tested with positive outcome in a number of short-term mutation tests (151, 168). Chromosome aberrations among degreasers were demonstrated in a German study from 1979 (92). Other experiments have raised suspicion of carcinogenecity, but epidemiological studies have not consistently shown an increased incidence of cancer or cancer mortality after exposure to TRI (13). This unclarified problem is of importance to questions of reproductive toxicity and potential carcinogenicity.

The purpose of the present study was to elaborate on the extensive outcomes of health effects reported from the literature of chlorinated solvents and TRI. The study population was chosen among metal degreasers, a group relatively monoexposed to chlorinated solvents with TRI as the dominant solvent. The intention was to contribute to the answers to the following questions:

1. Does long-term exposure to chlorinated solvents, especially TRI, as found in Danish workplaces from the beginning of the 1950's to 1984 in the metal industry, increase the risk of chronic organic brain damage?
2. Which psychometric tests are the most sensitive in assessing neuropsychological dysfunction in solvent exposed workers? How big is the influence of competing risk factors such as age, primary intellectual function, and education?
3. Do neurological outcomes such as cranial nerve disturbance measured by a clinical neurologic examination, still exist under present day exposure levels? And to what extent?
4. What is the relationship between acute/chronic exposure to TRI and to liver and kidney function, estimated by blood and urine laboratory tests?
5. Does high exposure to TRI cause mutagenic affection of germ and somatic cells?

This review summarizes a study of the broad spectered health effects of relevance to exposure to TRI. A perspectivation is made through an evaluation of the updated literature. The literature has been identified through the data bases TOX-line, NIOSH-TIC and CIS-abstract.
Finally an overview is given over the history of the solvent syndrome from the earliest medical descriptions to scientific and public recognition.

4.0. The history of chlorinated Solvents.

4.1. Organic solvents.

Organic solvent is the generic term for a collection of fluid chemical substances and compounds that share a common technical application: they are well suited for dissolving grease, oil, rubber, plastic, etc. Organic solvents are further characterised by the fact that they are easily evaporated, having a boiling point of no more than 200-250°C (78). In terms of chemistry, however, organic solvents do not constitute a homogenous group. Organic solvents are typically divided into non-substituted and substituted hydrocarbons.

Non-substituted hydrocarbons:	Aliphatic hydrocarbons (e.g. hexane)
	Cyclo-aliphatic hydrocarbons (e.g. cyclo-pentane)
	Aromatic hydrocarbons (e.g. toluene, xylene, styrene)
Substituted hydrocarbons:	Halogenated hydrocarbons (e.g. trichloroethylene, freons)
	Oxygenated hydrocarbons (e.g. ethanol, propylene glycol, acetone)
	Other hydrocarbons (e.g. acetonitrile, carbon disulphide)

Many non-substituted hydrocarbons are used in compounds. The best known example is white spirit, which contains about 50 different hydrocarbons. In comparison, the halogenated hydrocarbons are nearly always used in a pure, non-compounded form. This makes the halogenated hydrocarbons particularly suitable as the object of health-risk studies.

Some organic solvents are produced by the distillation of crude oil, while others, such as the halogenated hydrocarbons, are synthetic chemicals. The most commonly used organic solvents today were discovered midway through the 19th century. As industrial development accelerated, organic solvents were introduced to increase the speed and efficiency of a number of work processes. Chlorinated solvents were initially applied in the extraction of coffee and cocoa and for degreasing and cleaning metal components in the metal industry. The use of organic solvents has subsequently spread to practically all branches of modern industry.

The only reasonably large study thus far conducted in Denmark, which has attempted to shed light on representative consumption patterns in various branches of industry, was published in 1988 by The Danish National Institute of Occupational Health (131). The data was collected in 1985/86 and involved the participation of 664 companies from all branches. In 434 of these

companies, 1994 different fluid chemical products were used, and 3/4 of these contained organic solvents in a concentration greater than 1%. The most common applications were as cleaning, cleansing and degreasing agents, and as ingredients in paint, coolants, lubricants and so forth. Estimations based on this study suggest that about 420,000 persons, or 50% of those employed in manufacturing, construction, health services, service industries and maintenance, encounter organic solvents during a normal working day. Since the beginning of the 1960's, between 160,000 and 220,000 tons of organic solvents have been used per year in Denmark. According to information provided by industry itself, these overall consumption figures have remained more or less unchanged. There has been a trend towards a slight fall in overall consumption. The most significant change has been the substitution of the more toxic hydrocarbons, such as the aromatic and chlorinated hydrocarbons, with alcohols and glycols. Furthermore, improvements in occupational hygiene are continuously being made in the form of encapsulation, ventilation, etc.. The history of paint products resembles that of degreasing agents in terms of major changes in production technology and toxicology. In both cases the general course of events has involved development from water-based products to organic solvent-based products and back to water-based products again.

4.2. Chlorinated solvents.

Chlorine was discovered in 1774 by the Swedish chemist Scheele, when he observed the emission of a yellow-green gas after pouring hydrochloric acid over brownstone. A contemporary French chemist, Berthollet, examined the new element more closely. He found that it functioned extremely well as a bleaching agent for cloth. Textile fabrication was then a key industry in the industrial revolution. Chlorine absorbed in alkali became therefore one of the earliest industrially produced chemicals.

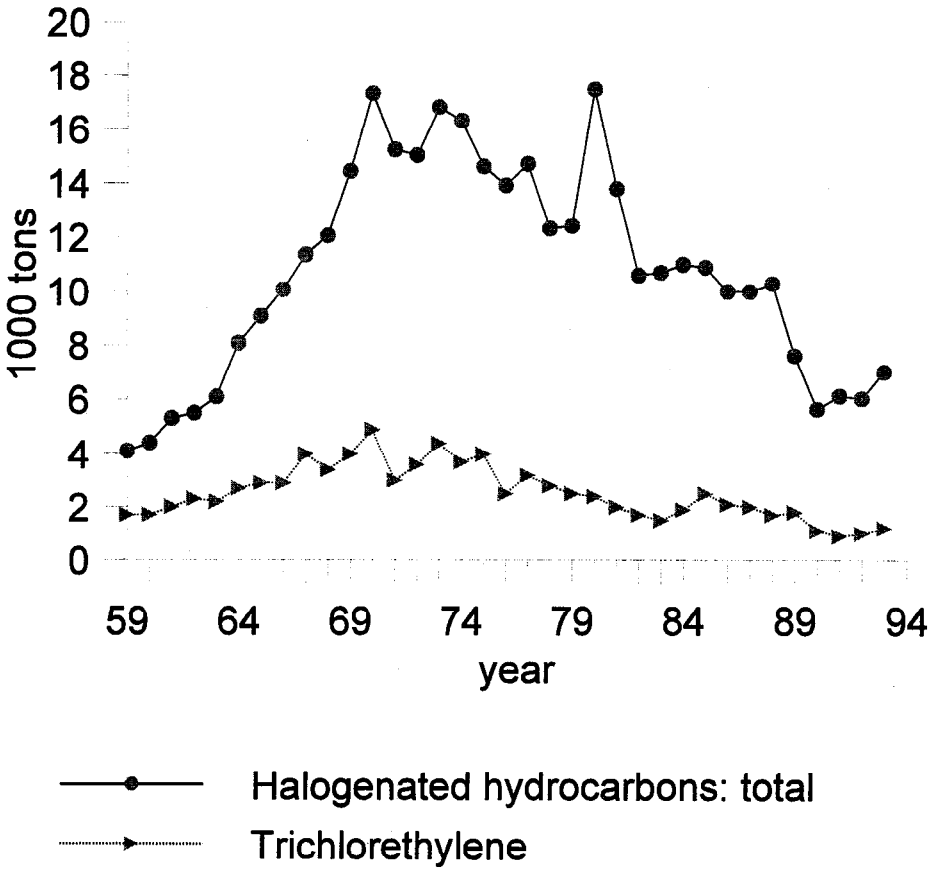
An important property of chlorine is that it can replace hydrogen in hydrocarbons. This substitution results in the transformation of hydrocarbons into chlorinated hydrocarbons. The first chlorinated hydrocarbon was 1,2 dichloroethane, which was manufactured in 1795. Other chlorinated hydrocarbons were discovered in 1821 (perchloroethylene) and 1864 (trichloroethylene). The production of chloroform for use as an anaesthetic was started in the mid 19th century. The first chlorinated hydrocarbon to be produced and used on an industrial scale however, was carbon tetrachloride, which was used from the 1890's to extract fats from vegetable

and animal products. Reports of massive toxic reactions soon appeared though, e.g. kidney failure, even after the use of modest amounts of carbon tetrachloride. It was therefore quickly replaced with trichloroethylene (TRI). TRI then became the dominant chlorinated solvent in the following decades, being used for the degreasing of metals, dry cleaning, as an ingredient in glue, as an anaesthetic, etc. Since the 1940's/50's a variety of other chlorinated hydrocarbons have replaced TRI in several of these processes (116).

Chemically, the chlorinated solvents belong to the halogenated hydrocarbons and are, as mentioned above, synthetic products. Halogenated hydrocarbons are derivatives of compounds consisting of carbon and hydrogen. The parent compound is usually a simple hydrocarbon such as ethylene (C_2H_4). The hydrogen in these compounds can be replaced by chlorine, or one of the other halogens: fluorine, bromine or iodine. Halogenated hydrocarbons contain one or more halogens as well as the parent hydrocarbon. The 5 most widely used halogenated hydrocarbons are the solvents trichloroethylene, perchloroethylene, methylene chloride, 1,1,1 trichloroethane and the group of chloromethanes and fluoromethanes known as freons. The first 4 are chlorine substituted hydrocarbons. The last group of chlorocarbon and fluorocarbon products are chlorine-fluorine substituted chemicals. The correct generic term is halogenated hydrocarbons. The better known term for these 5 substances, and the one which will be used here, is chlorinated solvents.

Chlorinated solvents, and chlorinated hydrocarbons in general, play a key role in today's international chemical industry. Chlorine is produced by the electrolysis of sodium chloride, while the hydrocarbons, the most important being ethylene, are products of the petrochemical industry. Chlorine and ethylene bound to 1,2 dichloroethane form the basis for the production of a long list of other chlorinated hydrocarbons, as well as for PVC, etc.. The manufacture of chlorinated hydrocarbons requires large scale industrial plants. The largest producing country is the USA. Danish consumption is totally dependent upon import. Figure 1, which is based on information from the Danish National Register of Statistics, illustrates the last 45 years of total halogenated hydrocarbon consumption, as well as consumption of trichloroethylene.

Figure 1. Consumption of halogenated hydrocarbons in Denmark 1959-94. Figures from the National Bureau of Statistics.



Trichloroethylene. TRI has been industrially produced since 1908. It quickly became the leading solvent for metal degreasing and dry-cleaning processes (116). TRI was also used in many other processes: in tanneries and the surface treatment of leather, as a cleaning fluid for film and printing presses, in the chemical industry, e.g. pesticide production, etc.. From the mid 1930's TRI was utilised as an inhalation anaesthetic. TRI was particularly suitable for orthopaedic surgery and obstetrics and was used in these fields until the start of the 1980's. TRI is nearly always used in a pure form- technical TRI though, contains less than 2% stabilizer. In the last 10-15 years, TRI has primarily been used for metal degreasing. For health reasons though there has been a trend to substitute TRI in this process with 1,1,1 Trichloroethane and freon 113. TRI has a number of technical advantages as a degreasing agent in the electronics and aeronautical industries: It degreases effectively without affecting the special alloys used in these industries. Experts in these branches expect a continued Danish consumption of about 1000 tons per year.

Perchloroethylene. Large scale industrial production of perchloroethylene, also known as tetrachloroethylene, dates back to the 1920's. Its main application has always been in dry cleaning. Perchloroethylene has been the dominant dry-cleaning agent in Denmark since the second world war. Following a short period of 6-10 years, when it was replaced by freon 113 in the dry-cleaning business, perchloroethylene has again become the leading substance in the mid 1990's (30). It is also used, though in modest amounts, for metal degreasing and in the manufacture of fluorocarbons. Danish consumption has fallen since the mid 1970's from about 3,000 tons to just under 1,000 tons per year. Due to the dry-cleaning industry's renewed use of perchloroethylene, an increase in consumption can be expected.

Methylene chloride. Dichloromethane is an often used synonym for methylene chloride, which, along with tri- and perchloroethylene, is one of the three classic chlorinated hydrocarbons that have been, and still are, utilized for many purposes in industry, trade and housekeeping. Methylene chloride is used as a varnish and paint remover, as an ingredient in glue, as a metal degreaser, as a component in foaming agents used in the production of polyurethane foam, and as the basis for synthesising other chemical substances. Consumption of methylene chloride has continuously increased to a level of about 1,200 tons per year in the mid 1980's. Since then, consumption has fallen slightly. Special toxicological conditions exist for methylene chloride. First, it evaporates very easily. Secondly, if it is absorbed by the organism, it is partly

transformed into carbon monoxide, which bonds with haemoglobin, thus reducing blood's capacity to transport oxygen. Evidence is accumulating that methylene chloride is carcinogenic. IARC classifies methylene chloride in the following manner: human evidence- inadequate; evidence based on animal studies- sufficient; evidence based on short term tests- sufficient / probable carcinogen. It may therefore be considered the chlorinated solvent for which there is most evidence of a carcinogenic effect.

1,1,1-trichloroethane. This has been employed commercially since the late 1940's for cleaning and degreasing in the metal and electronics industry, in glue, and as the basis for the production of vinyl chloride. 1,1,1-trichloroethane replaced TRI in the early 1980's in many degreasing operations; consumption in Denmark was by the mid 1980's roughly 1,200-1,500 tons per year. It was subsequently discovered, however, that 1,1,1-trichloroethane has the same degenerating effect upon the ozone layer as fluorocarbons. This resulted in both national and international measures to limit its use. From 1993, 1,1,1-trichloroethane could only be used in Denmark following special application for its use in laboratories, etc.. It has been totally forbidden to use it since the 1st January 1996.

Fluorocarbons. When fluorine replaces hydrogen in organic compounds, freons are created. The most widely used freons are freon 11, 12, 22 and 113. Freons were discovered at the start of the century, but it was not until the 1930's that their technical application became widespread. Their breakthrough was due to a cooperative effort from General Motors and the chemical company Dupont. The reason for this joint effort was the wish to mass-produce refrigerators and air-conditioning equipment, which could only be made possible if ammoniac and other poisonous substances, that had thus far been employed as coolants, could be replaced by less toxic alternatives. Their use as coolants has been the main area of application for freons. Since the late 1970's however, freon 113, which is the only freon that exists in a liquid state at room temperature, has been increasingly applied as a degreasing agent in the metal and electronics industry, with optical equipment, and, as mentioned, briefly in the dry-cleaning industry. Freons are also used as the propellant in aerosol sprays, in fire extinguishers, and as foaming agents in the plastics industry. The consumption of freons in Denmark peaked in the mid 1980's with about 5,000 tons per year. Since then a rapid fazing out of freons has occurred, both in Denmark and the rest of the industrialised world, because of their harmful effect on the ozone layer.

4.3. Chlorinated solvents and industrial processes.

Metal degreasing. The raw materials of the metal industry are nearly always covered in oil, primarily to protect the metal against rust. Degreasing can therefore be necessary at all stages of the production process. It is certainly always a requirement as a final step, prior to painting or testing and packing. Throughout the present century the traditional degreasing agent for minor jobs that can be accomplished with cold degreasing has been benzine and similar distillation products of crude oil. Here the item is lowered into a bucket or other small, open container and the oil removed manually with a brush or cloth. Since the 1920's/30's most medium-sized and large metal-working companies have employed vapour plants and chlorinated solvents as degreasing agents. The classic TRI-bath is an open container with boiling chlorinated solvent in the bottom. Unclean items are lowered into the container until they reach the vapour area above the solvent. The vapour condenses on the item, dissolves the oil and runs back into the container. The vapour tends to remain in the container (TRI-vapour is 3 times heavier than air). Above the vapour there is a cooling zone, where the TRI-vapours are condensed, and at the rim of the container there is an exhaust. Normally, one man is employed on a half or full time basis to operate such a TRI-vapour plant. The main exposure to TRI occurs when small reservoirs of TRI-liquid are raised in the hollows and indentations of the metal items, and when the residue oil is cleaned from the bottom of the bath. During the last 10-15 years, many companies have replaced open TRI-baths with partly closed baths, in which ventilation conditions are much better. A certain amount of risk for exposure remains though. The strongest technical trend concerning degreasing equipment over the last 10-20 years is towards product or method substitution. Degreasing in alkaline soap solutions, high pressure hosing with cold or hot water, or even the degreasing of painted items in rotating barrels filled with wood shavings, have usually been fully satisfactory, though slightly more time consuming alternatives. Companies working with special steel alloys, aluminium, copper, etc., have experienced problems with alkaline degreasing agents, in that they react with the metal. Thus, in these cases, and within the electronics and aeronautical industries, where degreasing needs to be completely dependable, TRI-vapour plants are still used in Denmark.

The history of degreasing agents can be more concretely illustrated by referring to events at a company that has participated in the present study. The example concerns a large yarn processing company with approximately 500 employees. Synthetic yarn and thread are heated, spun and

spooled before weaving. Spinning and spooling machines are typically 10-15 metres long and 2-3 metres high. The threads are led through the machinery with the aid of a mineral based spinning/spooling oil, leaving a layer of thread remnants and oil on the machine's surfaces. A team of cleaners consisting of 15-20 persons is employed full-time with the task of degreasing the machinery. As a cleaning agent the company used an organic solvent poured into litre measures. The machines were cleaned with paint brushes that were continuously dipped into the cleaning fluid. Particularly soiled machine parts, and finally the floor, were doused with solvent from the litre measures or buckets. The amount of cleaning fluid used per day by each cleaner was typically 5-10 litres, the exact amount being dependant on the individual's tempo and procedure. Throughout the 1960's petroleum was used for machine degreasing, until a worker returned one day from his lunch break with a cigar in his mouth. The petroleum fumes ignited, leading to a fire. Consequently, the company substituted petroleum with 1,1,1-trichloroethane. Chlorinated solvents are not flammable, and insurance companies at this time even encouraged the use of chlorinated products by reducing insurance costs for companies who adopted their use.

However, the cleaning procedures outlined above meant that a high level of exposure was quickly reached. In the summer of 1975 the cleaners showed various symptoms of poisoning; on one occasion several of them experienced reduced levels of consciousness, while others passed out. 1,1,1 Trichloroethane concentrations of up to 750 ppm were measured (the acceptable limit at that time was 100 ppm and is now 50 ppm). The trade union became involved and a safety consultant discussed the possibility of a work stoppage on the grounds of "threats to life, limb and well-being". On the advice of The Working Environment Service, the company replaced its degreasing agent with freon 113, which at this time was considered to be extensively nontoxic. Cleaning procedures and thereby exposure remained, however, unchanged. Work-hygiene measurements were made in 1983, in connection with the present study, revealing air concentrations of freon 113 of 260-420 ppm. At the same time, medical and psychological tests concluded that 8 out of 23 cleaners had suffered brain damage, 3 of these solely as a result of exposure to freon 113. The company then changed to using alkaline soap, which was completely free of organic solvents. Some difficulties were experienced in the beginning; the cleaners had to rub and scrub somewhat more, but the final result was fully satisfactory. The company has employed this cleaning agent since 1983.

Dry cleaning. During dry cleaning, clothes are soaked in solvent in a closed washing machine. This lasts for 10-15 minutes. The clothes are then centrifuged and blow-dried. The entire process is contained within a closed cycle, so that most of the solvent is recycled. Earlier, the clothes were centrifuged in open centrifuge machines and the clothes hung to dry either indoors or outdoors. Until the mid 1960's work hygiene standards at many Danish dry-cleaning establishments were poor; seepages occurred from leaky equipment and further exposure resulted when the equipment was cleaned. Solvent exposure in Danish dry-cleaning companies today is presumably modest. In a survey of the dry-cleaning branch conducted in 1985-86, 350 dry cleaners with approximately 900 employees were found (30). 65% of these companies used perchloroethylene, 30% used freon 113, and 5% used white spirit. Since January 1995 the use of freon for dry cleaning has been prohibited, because of its effect on atmospheric ozone, so perchloroethylene is now virtually the sole substance used.

Adhesion processes and paint removal. When furniture is upholstered, foam plastic is fastened to the framework with glue. In the metal industry, the joining of thin sheets, attachment of axels, and so on, is often achieved with the use of a strong adhesive. Various adhesion processes in the paper and cardboard industry require fast drying glue. Ten years ago, these three areas employed vast quantities of adhesives containing chlorinated solvents, predominantly trichloroethylene and 1,1,1-trichloroethane. There has without any doubt since then occurred a marked substitution. Adhesives containing chlorinated solvents are primarily used today for particularly demanding tasks that are only rarely carried out.

Paint remover, which has traditionally contained 70-80% methylene chloride and 20-30% methyl alcohol, is used to remove old paint and varnish. The use of these products today is estimated to be modest. A change has occurred towards the use of soda lye, or to the removal of paint by burning.

Foam plastic production. When polyurethane foam is manufactured, e.g. for use as foam rubber cushions or pipe insulation, polyole mixed with isocyanate has to be inflated. For many years, this has been done by using chlorinated solvents: freons, 1,1,1-trichloroethane or methylene chloride. Out of consideration for the environment there have been demands for substitution, and during the last 3-5 years chlorinated solvents have been completely removed from this industrial process in Denmark. Today, PU-foam is inflated with halogenated hydrocarbons, that do not affect ozone, such as "soft freons", e.g. HFC. Substitution to carbon dioxide is, however, on its

way.

Air conditioners, refrigerators and freezers. During a 30-40 year period, freons, and to a lesser extent other chlorinated solvents, have been the preferred cooling agent in refrigerators and deep-freezers. Approximately 1,000 persons are employed in the assembly of this equipment in Denmark. In some cases exposure is on a daily basis and in the case of large, industrial equipment, dosages may be quite substantial during evacuation and pressure checks related to repair work. Since January 1995 there has been a total ban on the use of the hard freons (freon 12 and 502) in refrigeration and freezing equipment. Today, halones, bromide substituted CFC compounds are the most commonly used cooling and freezing agents.

Other areas of application. Apart from the areas named above, chlorinated solvents are also used in many settings where amounts, and numbers of exposed persons, are relatively small. Examples include its use in the processing of medical products, the chemical industry and in industrial and research laboratories.

5.0. Basic toxicological information on trichloroethylene.

TRI (C_2HCl_3) is a colourless, non-flammable liquid with a boiling point at 87,0° C and a vapour pressure (20° C) of 58 mm Hg. The odeur threshold is 28 ppm. In most Western countries the threshold limit values of TRI are at 20-30 ppm - in Denmark the threshold limit value (TLV) has been 30 ppm from 1954 to jan 1994 where it was lowered to 10 ppm. Today TRI is nearly exclusively used for metal degreasing; in the USA 90-95% of the produced TRI is for various purposes of degreasing.

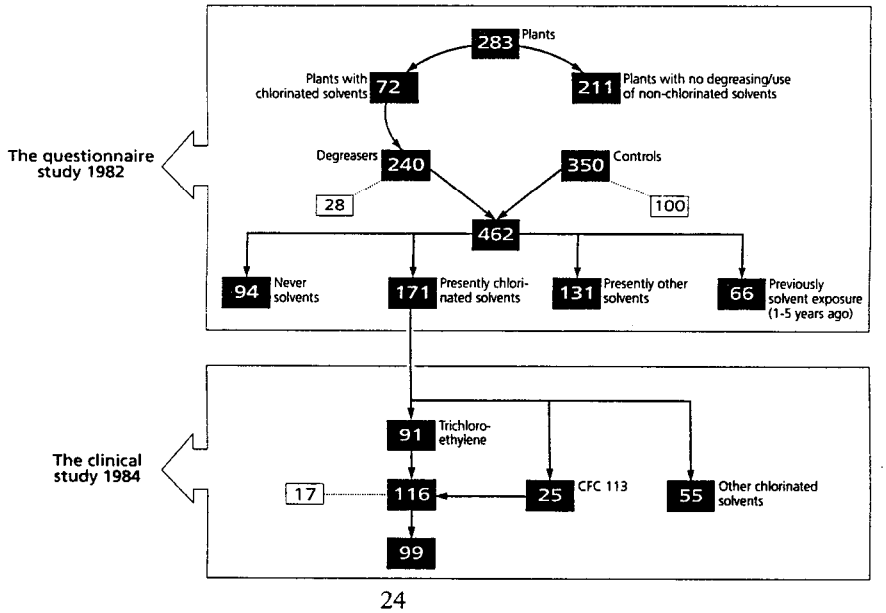
TRI in contact with open fire as welding and smoking decomposes to the lung toxic substances hydrogenchloride and phosgene. In contact with alkali, TRI decomposes to dichloroacetylene which is highly neurotoxic (151).

Inhalation is the principle route of concern by which TRI enters the body, harmful effects from skin absorption can hardly be expected in the occupational setting (56). TRI distributes widely into body tissues. The partition coefficient for blood/air is 8-10 and for fat/blood 24. TRI is eliminated by 2 major processes, pulmonary excretion of unchanged TRI and liver metabolism to urinary metabolites. At air concentrations of 500 ppm or less humans are estimated to metabolites between 60 and 90% of absorbed TRI (34, 56, 120). In the liver TRI is first metabolized to chloral hydrate and to reactive epoxide by the microsomal P_{450} system. Metabolism of TRI is enhanced by some drugs g.g. barbiturates. Hydant toxicity can result from drug interactions known to occur with e.g. ethanol and disulfiram (56). About 50% of the absorbed amount is excreted in the urine as TCE with a biological halflife of 10-15 hours, while 10-30% is excreted as TCA (120, 121). As TCA is bound to plasmaproteins, it is excreted slowly by the kidneys with a halflife around 100 hours. In this way TCA has a tendency to accumulate in the body. Urine-TCA of exposed workers is the most reliable parameter of biomonitoring reflecting exposure through the last 1-2 weeks (44). After a mean exposure of 30 ppm of TRI in the air during the course of 4 to 5 hours, a TCA-value in the range of 65-85 mg/l will appear (151). It appears from current knowledge from animal studies that metabolites of TRI rather than the parent compound are responsible for cytotoxicity and carcinogenestic in the liver and kidney, while central nervous system depression is believed to be caused primarily by TRI. Pathophysiologic mechanisms are basically unknown - a theory behind cranial neuropathy is discussed under chapter 8.2.

6.0. Study design and material.

The investigation was undertaken in a geographically well-defined area, district number 2 of the metal workers' union, corresponding to the county of Aarhus with some small extension. The area has a population of 600,000 people in a typical Danish industrial structure of small and medium-sized plants. The target group of the study was metal workers degreasing in chlorinated solvents. The initial intention was to contact all metal degreasers in this area. The best coverage of registered plants was found to be in the wage statistics of the metal workers' union, where 263 plants were identified. We supplemented with 20 metal factories by using company lists delivered from The National Labour Inspectorate and chemical companies selling degreasing solvents. Data collection was a two stage procedure. The 283 metal plants contacted were requested to fill out a questionnaire with information on degreasing products used in each plant, requesting names and addresses of the degreasers engaged presently or previously with exit over the last 5 years. This information was obtained from all 283 plants resulting in 240 degreasers using chlorinated solvents at 72 plants (Fig. 2). The primary investigation group of those 240 degreasers was compared to a control group on 350 workers randomly selected through card files of semiskilled trade unions in the same geographical area. The introductory study was a cross-sectional questionnaire-based study on neuropsychological symptoms which was performed in 1982 with the participation of 462 workers (78,3%).

Figure 2. Diagram of the study population.



A clinical study was then set up with the purpose of performing a detailed clinical epidemiological study primarily of subjects exposed to TRI, the classical chlorinated solvent, still in widespread use and with toxicological outstanding points. A minor factory cohort of CFC exposed individuals were included as there has been a trend to substitute TRI and 1,1,1-trichloroethane by CFC 113 for degreasing and cleaning. All degreasers from the questionnaire study who were engaged with TRI or CFC 113, either presently exposed or having ceased in the degreasing job within the last year, were selected for a one-day clinical medical and neuropsychological examination at a hospital department of occupational medicine. Of 116 persons eligible 16 declined to participate, and 1 had died of non-occupational reasons (Fig. 2). The total number of participants in the clinical study was 99 persons, a participation rate 85,3%. The age range of the material was 19-68 years, mean age 39,4 years - 90 were males, 9 were females.

The clinical study was performed in 1984-85 and was a follow-up of the cohort of metal degreasers from 1982. The study design is a cohort study with one single follow-up after 2½ years. There was no external control group. However, all 116 degreasers who fulfilled the criteria were included independent of the duration of exposure. The range of full-time degreasing was from 1 month to 36 years, which means that internal groups of comparison could be established, suitable for dose-response analysis.

7.0. Methods.

7.1. Exposure assessment.

Metal degreasing was done in pure solvent, either in a vapour plant or as cold-degreasing with a brush in an open vessel or in a bucket. A few bigger plants used a closed washing-machine. In our experience, based on factory inspection, some work environment measurements and systematic biological monitoring, these degreasing methods do not differ substantially in terms of exposure strain. The actual strain is determined by factors such as the shape of the metal items (hollow items contain condensed solvent after degreasing) or the mode of administration Highest exposure is met during maintenance and cleaning inside the vapour plant itself. Exposure assessment in this study was done by three completing approaches:

- review of nationwide measurements of thrichloroacetic acid notified to the Danish Labour Inspection Service during 41 years. The object was to obtain an impression of trends in biological exposure levels by metal degreasing.
- detailed interview of degreasers about previous solvent exposure forming a basis for an estimate of individual accumulated solvent exposure.
- current levels of TRI metabolites TCA and TRI in both blood and urine. These biological monitoring data was sampled at the day of clinical examination to express present exposure strain.

To elucidate long-term exposure levels, historical exposure data of TRI has been reviewed, comprising all measurements of TCA in urine that was reported to The Danish National Labour Inspectorate during the period 1947-87 (study VII). For the metal industry this was 1544 values of biomonitoring from 147 companies. The mean value was 48 mg U-TCA/l range 0-1975 mg/l. From the mid 1950's to the mid 70's the Danish exposure level of TRI for metal degreasing seems to have been fairly constant, corresponding to about 40-60 mg/l urine-TCA (VII). For full-time TRI degreasers, this corresponds to exposure levels in air around 2/3 of the TLV at 30 ppm. Before that the exposure level was higher, while it was rapidly declining after the late 1970's (VII). The mean value of TCA in 1947 was 80 mg/l, while at the end of the period in 1987 it had decreased to 18 mg/l.

In the introductory questionnaire study comparisons were made between sampled groups of exposed vs. unexposed persons. In the dose-response evaluations the exposure variable was based on summation of questionnaire data on the intensity of degreasing (hours/week) times the duration (number of years).

In the clinical study a detailed life-long occupational history was taken including information on types of solvents used during number of hours/week and number of years, together with general hygienic working conditions. The criteria for inclusion were intended to create a group of persons who were singly exposed either to TRI or CFC 113. However, in studying chronic toxic encephalopathy, the relevant exposure measurement is the life-long cumulated exposure. Some had previously degreased using aliphatic solvents such as thinner or white spirit, whereas only a few had previously been industrial painters. The dominant exposure was trichloroethylene for 70 workers and CFC 113 for 25 workers.

On the basis of a thorough occupational interview of the degreasers a cumulative exposure index was calculated using number of hours of work with degreasing or other direct solvent exposure per week, multiplied by number of years of exposure, multiplied by 45 working weeks/year. Such a semiquantitative estimate of solvent exposure based on duration and intensity (average exposed hours) has been the main constituent of newer epidemiological solvent studies (111, 117). From this estimation of the total number of exposure hours, 3 exposure groups were established with mean years of full-time solvent exposure of 0.5 year and 2.1, and 11.0 years respectively (table 1). This exposure categorisation might freely be transformed to what is probably a more common work schedule for a degreaser: half-time degreasing and half-time working with transportation, as a storeman etc. Under that assumption the mean years of cumulative solvent exposure in the three exposure groups becomes 1.0 year and 4.2 years and 22.0 years respectively.

Table 1. The clinical study group. Cumulative exposure and age. N = 99.

		Age		Number of years with full-time solvent exposure	
Exposure groups	Number of persons	mean	range	mean	range
Low	21	34.5	19-59	0.52	0.05-0.9
Medium	37	35.7	19-59	2.2	0.91-3.8
High	41	45.2	25-68	11.0	4.0-35.6

Current or recent exposure to TRI was quantified by blood and urine analysis of the metabolites TCA and TCE. Only for the 6 persons presently exposed to TRI more than 30 hours a week, was a substantial biological exposure level found with urine-TCA, mean and range: 7.7 mg/l (1.1-26.9) and blood-TCA, mean and range: 6.5 mg/l (2.3-14.1). For 6 persons exposed 6-29 hours a week, U-TCA was 1,9 mg/l (1.4-7.8) and B-TCA was 2.4 mg/l (1.1-5.8). For 55 subjects of the study population the U-TCA was below 0.02 mg/l, which is the limit of detection in the U-TCA analysis. These comprise workers who had ceased with TRI-exposure at the time of the clinical follow-up (46 subjects), or low exposed workers (9 subjects). The U-TCE showed to be the parameter with strongest correlation to the anamnestic information of number of hours of weekly exposure. A finding that strengthens the availability of U-TCA as the single parameter most often used for biological monitoring of TRI-exposed workers.

There were not any systematic air measurements during the long relevant exposure period. However, 23 of the 25 CFC-exposed workers came from a single large textile plant where degreasing of spinning machines with pure CFC 113 was done with the solvent poured into a 1 litre jug and applied with a brush. No local ventilation system was available. The weekly usage for workers in this CFC-cleaning procedure was 40-65 litres for the most of the study period. After safety instructions of the workers 1-2 years before the clinical study in 1984 the daily consumption per worker was reduced to 5-10 l. Still measurements of the work environment in that plant in 1984 showed time-weighed average concentrations in the breathing zone of 260-420 ppm; which can be compared with the US and Danish TLV for CFC of 500 ppm.

7.2. Questionnaire investigation.

The self-administered questionnaire in study I contained among other things 27 questions concerning health and work environment information of solvent exposure. The health questions were based on the Swedish "Örebro-questionnaire" combined with later Danish questionnaires on organic solvents (84). Included were questions of acute and chronic neurological, neuropsychological and neurophysiological toxicity.

7.3. Medical interview.

The clinical study included 98 variables with information on previous hospitalizations, present symptoms of ill health and detailed data on confounding. The focus was put on symptoms of mental impairment: tiredness, lack of initiative, reduced learning, impaired memory, impaired attention, and psychomotoric function, change in mood, anxiety and nervousness, emotional

lability and irritability. The anamnesis and the clinical examination was taken by the same physician (KR).

7.4. General clinical examination.

The examination consisted of measurement of systolic and diastolic blood pressure, inspection of the oral cavity, stethoscopy of the heart and lungs, palpation of the abdomen, and physiurgic examination of the upper musculosceletal system. This was supplemented with electrocardiography in 9 leads and measurement of lung function with a computerized spirometer.

7.5. Neurological examination.

The neurological examination consisted of qualitative examinations of cranial nerve function, coordination, reflexes, sensibility and muscle strength. The function of the olfactory nerve was tested on each side separately by the successive blind presentation of ground coffee, lavender, solution and petrol. For testing the sensitive function of the facial nerves, subserving taste, we used solutions of saccharhine, NaCl, citric acid, monohydrate and kinin chloride.

The coordination tests assessed tremor, finger - nose coordination, heal - knee coordination, diadochokinesis, Romberg test and gait.

Vibration threshold, as a proxy variable of sensory neuropathies was measured by a biothesiometer at 8 locations: the second fingerpulp, the distal styloid of the radius bone, the medial maleolus, and the first toe pulp, all bilaterally.

A rationale behind choosing these test entities among several potentially relevant neurological tests is as follows. Cranial neuropathy is the neurotoxicological outcome related to TRI exposure reported currently through most of this century, not only affecting the trigeminal nerve but also the cranial nerves (I, VII, X, XII) (59, 99, 154). A marked affection of motor dyscoordination has been demonstrated in a recent well-designed Danish study (117). Impaired vibrotactile since has been claimed to be an early indicator of sensory neuropathy (112).

7.6. Neuropsychological examination.

The psychological examination consisted of performance in neuropsychological tests together with a clinical observation of behavior during the test situation. The psychological examination,

all by the same psychologist (HJJ), were performed under a blind procedure, where the psychologist did not ask and was not informed about the occupational exposure or medical symptoms. The daily examination started with a joint meeting between the MD, the psychologist and the two test subjects, where the examination programme was ruled out and the test subjects explicitly asked not to tell the psychologist about symptoms and complaints for working conditions. So, the test score was unbiased to knowledge of exposure for disease, it was based exclusively on the test performance.

The test battery consisted of 15 subtests from WAIS and Luria in combination with tests developed in Finland, Sweden and Denmark in the context of occupational medicine (1, 35, 43, 89, 100, 161, 175). The psychometric tests used were WAIS vocabulary in the original WAIS version: single reaction time; acoustic-motor function; discriminatory attention; sentence repetition (revised Benton); PASAT (modified version); digit span; Text Repetition; Rey's auditory verbal learning test; visual gestalts; stone pictures (memory test developed for this investigation); the digit symbol test from WAIS; revised Santa Ana Dexterity; motor function ad modum Luria; Mira (psychomotor ability without optical control). For further description of the psychometric tests applied there is referred to study III.

The psychometric test scores included in the statistical analyses in study III are unadjusted raw scores.

The final clinical assessment of the degree of psychoorganic syndrome was based on integrated information about the history of mental impairment, performance in psychometric tests, and clinical signs of demential behavior. The psychometric test scores used in the clinical assessment of psychoorganic syndrome were adjusted for the effect of age, primary intellectual function, and word-blindness (II).

7.7. Blood and urine tests.

The purpose of the blood and urine analysis was partly to assess biological levels of solvent exposure, and partly to screen for solvent affection of liver and kidney function. Biologic exposure levels were measured by the blood content of TRI, TCA and TCE plus the urine content of TCA and TCE. Blood samples were analysed for: S-aspartate, S-aminotransferase, S-gamma-glutamyltransferase, S-alkaline phosphatase, S-bilirubin, S-protein, and P-protrombin. Determination of liver function tests was carried out by conventional methods.

The activity of N-acetyl-β-glucosaminidase (NAG) in the urine was analysed as an indicator of injury of the renal tubular cells. Urinary NAG activity was measured with a fluorometric assay -

urinary creatinine was used for correction of differences in urine flow (115, 182). Additionally the kidney function was evaluated by urine microscopy for erytrocytes and qualitative analyses for protein and glucose.

7.8. Genotoxic examination.

All 15 workers presently degreasing with TRI more than 20 hours/week were included in this part of the study. The genotoxic examination consisted of 2 parts. First semen specimen, which 13 of 15 workers agreed to deliver. Analysis was made for common quality parameters: count, volume, motility, and morphology - as recommended by WHO (180). After staining with quinacrine dihydrochloride a minimum of 500 sperm was scored for each sample to determine the proportion of mature spermatozoa containing 0, 1 or 2 fluorescent Y-bodies - as described by Kapp and Jacobsen in 1980 (90). The presence of 2 fluorescent bodies (YFF%) in a normal-sized spermatozoa may indicate the presence of 2 Y-chromosomes resulting from a chemically induced event during the second reduction division (174). 14 non-exposed physicians working at university institutions served as controls. The second study parameter in the genotoxic examination was unstable chromosome aberrations in lymphocytes from cultured blood samples. 100 metaphases per subject were analysed for structural aberrations (breaks, gaps, translocations, deletions, inversions) and hyperdiploid cells. As reference material a currently sampled group from population surveys and parents of offspring without stable chromosomes abnormalities were used (127). This group comprised 669 persons, with 7,889 metaphases being analysed.

7.9. Confounding variables.

The confounding variables are variously included in the analysis depending on outcome variables of the single studies. The following 8 variables were, according to biological plausibility and knowledge from previous studies, considered as potentially competing risk factors: age, primary intellectual level, word blindness, education, history of arteriosclerotic disease, history of neurologic/psychiatric disease, alcohol abuse, and current exposure to organic solvents.

Age is a potentiel confounder to most of the investigated associations in these studies: neuropsychological, neurological, as well as the liver and the kidney outcomes. When studying the relationship between age and psychoorganic syndrome, using age a continuous variable, one could assume a linear relation. Biological plausibility, however, would indicate an S-shade relation. Initial analyses by 10 age groups showed 40 years as an inflection point, with a high degree of association at 40 + years. This is the rationale behind the 3 age groups in the logistic

regression analysis: > 29 years, 30-39 years, and 40 + years. In the multiple regression analysis age is used as a continuous variable.

The primary intellectual function is necessary to take into account when assessing present performance in neuropsychological tests. The WAIS vocabulary test has shown to be resistant to the effects of solvents and is here used as a single proxy variable for primary intellectual level. The age-standardized scale score, after US-standardization of age adjustment, was used.

Word-blindness may affect phoneme discrimination and the performance in psychometric tests, especially auditory immediate memory tests as digit span and sentence repetition. 14 persons were recorded as word-blind on a basis of self-reported previous and present dyslexia. The level of *education* may also exert a confounding influence on neuropsychological performance. Of school education and skilled education, the former had the strongest effect in bivariate analysis, and was so chosen as the education variable. There were 20 persons with more than 9 years of basic school and high school education.

The presence of systemic arteriosclerosis indicates a risk of cerebral affection. The variable *arteriosclerotic disease* comprised a positive history of present symptoms or objective signs of systemic arteriosclerosis. This group consisted of 14 persons with intermittent claudication, angina pectoris, acute myocardial infarction or electrocardiographic signs of coronary arteriosclerosis. None of the subjects had anamnestic information on stroke and transient cerebral ischaemia.

Considered as subjects with relevant neurological disease where 5 persons with post-concussional symptoms lasting more than 3 months and 1 with former grand mal epilepsy - none had a history of neuroinfections. These 6 persons, together with 4 persons with former primary psychiatric disease of depressive character (2 of them under present psychopharmacological treatment) and 1 person with slight mental retardation, were given a positive value for a confounder variable designated *neurologic/psychiatric disease.*

Of relevance in these studies alcohol exerts a damaging effect to the nervous system and the liver. With regard to *alcohol abuse* as a confounding variable the limit was chosen as a weekly mean consumption of more than 21 drinks or periods as an alcoholic defined as periods with

treatment for alcohol abuse. This variable included altogether 5 persons.

The narcotic effect of current solvent exposure is able to mask the effect of chronic solvent exposure in the neurotoxicological studies. *Present solvent exposure* was considered a potential confounding variable - 53 persons were currently exposed or exposed during the previous month.

7.10. Statistical analysis.

Discrete variables were analyzed by χ^2test, Fisher's exact test and $\hat{\chi}$ -trend test. Confounder analysis was initially made by stratification followed by Mantel Haentzel's test for stratified analysis and final confounder adjustment was made by logistic regression analysis where odds ratios were estimated by the variables forming part of the multiplicative model (31).

Continuous variables were analysed by analysis of variance, the Mann Whitney Rang Sum test, Student t-test and linear regression analysis (11). Control of confounding was achieved by multiple regression analysis of continuous variables. The statistical analysis was performed with a computer programme SPSS/PC.

8.0. Results and discussion.

8.1. Neuropsychological dysfunction.

8.1.1. Questionnaire study.

Chronic brain dysfunction is a key issue in relation to solvent exposure. We started our series with an assessment through questionnaire studies (I, 139, 140). Ten symptoms concerning memory, concentration difficulties, fatigue, irritability, alcohol intolerance, and disturbance of sleep comprised the chronic neuropsychological symptoms. Prevalence proportion ratios of 1.6-3.9 of the single questions were found between the primary exposure group of 171 persons and a control group of 94 persons never exposed to solvents (I). TRI was more closely associated with inconveniences and symptoms than 1,1,1-trichloroethane, methylene chloride and CFC 113. A significant dose-response relation could be demonstrated. After adjustment for possible confounding in logistic regression analysis there appeared to be a significant association between an index of chronic neuropsychological symptoms and present medium/high exposure (OR = 3,4), previous exposure to solvents (OR = 4.2), and consumption of alcohol (OR = 2,2).

In Pearsson correlation analysis as well as profile analysis we have validated the quality of the single questions in the questionnaire in relation to measuring the effect of exposure. Approximately all information was contained in 6 out of 10 chronic neuropsychological questions. These were: 1) "Do you feel that you have become forgetful?", 2) "Have you been told, at work or at home, that you have become more forgetful?", 3) "Do you often go back and check something you have done already, like having locked the door?", 4) "Do you have difficulty in concentrating?", 5) "Do you get more easily irritated over minor things than before?", 6) "Do you more easily get intoxicated by alcohol than before?". These six questions are recommended to be included in future questionnaire studies on neuropsychological outcome.

Discussion.

A questionnaire study of the hypothesized question of chronic cerebral dysfunction has major draw backs. There are problems with the measurement of the effect variable. "Psychoorganic syndrome" cannot be diagnosed through a questionnaire. The neuropsychological questions are probably sensitive, but fairly non-specific proxy variables potentially affected by information-bias. We are interested in first and foremost a chronic state of CNS toxicity and this question of reversibility will tend to give an overestimation of prevalences and risks in the cross-sectional study as we are dealing with the sum of acute and chronic exposure. Some other problems of

confounding can be dealt with through analysis. However, confounders such as alcohol consumption must be anticipated to be difficult to measure accurately in questionnaires, and others such as premorbid intellectual function, are nearly impossible to measure in a questionnaire. Secondary healthy worker selection tends to bias towards the null-hypothesis, when we investigate workers in job.

Findings of high frequencies of neuropsychological complaints, as in this study, have been confirmed in questionnaire studies from Scandinavia, as well as many other industrial countries throughout the last 20 years (26, 77). Most of these studies included control groups, many also adjustment for the effect of confounding control, but nevertheless there might be severe affection of the types of bias described above. Still questionnaires may play a role in health surveillance of exposed workers. A recent Swedish study indicated psychiatric symptoms as earlier indicators of adverse effects than a psychometric screening test battery (52).

8.1.2. Psychoorganic syndrome.

Weaknesses concerning validity in the questionnaire study are taking into account in the clinical study (II), some more successfully than others. This discussion will be expanded upon below.

The principle outcome variable of this study was psychoorganic syndrome, a mild syndrome of dementia characterized by cognitive impairment, personality changes and reduced motivation, vigilance and initiative. Development of a characteristic symptom picture and neuropsychological test results are crucial to the diagnosis. The quantitative psychological data of psychometric test performances constitute an important foundation for the diagnostic conclusion. For this research project tests are sampled and scored by the psychologist having no knowledge of occupational exposure or symptoms. However, the overall assessment of the degree of psychoorganic syndrome was made by the two clinical investigators together (psychologist and MD). Clinical signs of demential behaviour, history and degree of symptoms of mental impairment were evaluated in relation to test performance and were used in the interpretation of the test results in the final assessment of the degree of psychoorganic syndrome. The degree of psychoorganic syndrome (demential score) was grouped in "no", "suspect", "mild", "mild to moderate", "moderate", "moderate to severe", and "severe". This graduation is an extension of a 3-scale graduation in mild, moderate and severe dementia orginally described by Lishman (106) and Bruhn (35).

Comparison and transposition between the Danish 6-scale and the WHO 3-scale of solvent syndrome from 1985 is not simple and easy. A joint WHO/Nordic Council of Ministers Working Group recommended a categorisation into three types of chronic organic mental disorders: organic affective syndrome, mild chronic toxic encephalopathy and severe chronic encephalopathy (181). Later in 1985 proposals from a US workshop operated with similar classification scheme adding a new initial type with mild reversible symptoms, making four types of neurobehavioral disorders altogether (18). Our "suspected" psychoorganic syndrome corresponds mostly to the organic affective syndrome of WHO with subjective symptoms of chronic neuropsychological nature and no or few psychometric test abnormalities. Our categories "mild" and "mild to moderate" corresponds mainly to the mild chronic toxic encephalopathy of WHO with relevant symptoms as well as general tests deficits, especially concerning psychomotor function, perceptual speed and memory. We found no cases of psychoorganic syndrome more severe than "mild to moderate".

Among the metal degreasers, the prevalence of "mild" or "mild to moderate" psychoorganic syndrome was 10,5% for those with low exposure category, 38,9% for medium exposure and 63,4% for high exposure (II). Of 42 persons with psychoorganic syndrome, 31 had been predominantly exposed to TRI and seven had exclusively been exposed to TRI. Of the 25 persons exposed to CFC 113, 8 had psychoorganic syndrome. Three had exclusively been exposed to CFC 113, and these have been reported separately as the first cases in the literature of clinically diagnosed cases of chronic toxic encephalopathy after CFC exposure (141).

The data do not allow more specific conclusions about the dementias in using potential of single solvents. The predominant exposure were trichloroethylene and CFC 113, but many of the workers also had some additional exposure to aliphatic or aromatic hydrocarbons.

Logistic regression analysis was performed with subjects of low exposure (< 1 year of full time exposure) as reference group. It appeared that there was an increased risk of developing psychoorganic syndrome after solvent exposure (table 2). After adjustment for 6 potential confounders, however, the association was significant only for the highest exposed group, who had an average full time exposure of 11 years. The risk of psychoorganic syndrome increased significantly with increasing age and decreasing performance in the WAIS vocabulary test, used

as proxy variable for primary intellectual function. None of the other potential confounders had any significant effects on the risk of developing psychoorganic syndrome (table 2).

Table 2. The risk of psycho-organic syndrome associated with cumulative solvent exposure after adjustment for six confounding variables by logistic regression analysis. (N=96). Low solvent exposure was used as reference.

	Unadjusted values		Adjusted values	
Variables	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval
Solvent exposure				
Low	1.0	-	1.0	-
Medium	5.4	1.1-27.1	5.6	0.93-34.3
High	14.7	3.0-72.8	11.2	1.9-66.6
Age				
≤ 29 years	1.0	-	1.0	-
30-39 years	1.8	0.46-7.3	2.0	0.4-9.2
40 + years	10.3	3.0-35.6	16.1	3.4-77.2
Primary intellectual level (WAIS vocabulary)	0.85	0.67-1.1	0.62	0.45-0.87
Arteriosclerotic disease	2.7	0.82-8.7	.	
Neurological/ psychiatric disease	1.6	0.46-5.8	.	
Alcohol abuse	0.85	0.14-5.3	.	
Present solvent exposure	0.95	0.42-2.1	.	

The relation between sex and psychoorganic syndrome was 40/87 46% men and 2/9 22% women with psychoorganic syndrome. The mean duration of solvent exposure was 5.4 years for men and 6.4 years for women. The observed difference of the relationship between sex and psychoorganic syndrome was not statistically significant, and may be due to change.

The predominant confounders were age and WAIS vocabulary. Age gives bias away from the null-hypothesis. WAIS vocabulary gives bias towards the null-hypothesis. As both the

confounding variables were significant, the statistical analysis indicated that age and primary intellectual level had not been adequately considered in the interpretation of test performance in terms of mental impairment; i.e. in the dementia score where an adjustment of raw scores were made concerning age and primary intelligence. The consequence of this systematic error in dementia scoring is an overestimation of mental impairment in subjects with a low WAIS vocabulary score or high age and vice versa an underestimation of mental impairment in subjects with high WAIS vocabulary score or low age. The relations between solvent exposure, age and psychoorganic syndrome has been further elucidated by statistical analysis. Mantell-Haentzel analysis of the effect of solvent exposure adjusted for age gave a adjusted OR of 10.8 while the relation between age and psychoorganic syndrome controlled for levels of solvent exposure corresponded to a adjusted OR of 6.3. This trend to a slightly greater effect of solvent exposures over age is in accordance with findings in the logistic regression analysis. The role of interaction between these 3 variables has been ruled out. No interaction was found, so the actions of age and solvent exposure in relation to psychoorganic syndrome are conceptually independent.

Discussion.

Study II has strengths and weaknesses. Among the advantages counts a population of workers mainly monoexposed to single solvents, TRI or CFC 113. The inclusion of unselected metal degreasers from a confined region has the aim of restricting selection bias, although the short follow-up-period of 2.5 years for this cohort gives a limited guarantee for control of secondary healthy worker selection in this period. The vast range of exposure from 1 month to 36 years makes this study group suitable for dose-response calculations in examining questions of causal relations. The absence of a control group is not by all means a draw back. Studying psychoorganic syndrome, we deal with a "soft" outcome variable with many relevant confounders that are difficult to take into account by an external matched control group. However, a control group would have given possibility to match by matchable confounders as age and education. The relationships between solvent exposure and psychometric tests considering the effect of age could be analysed by greater strength with an unexposed external group in stead of an internal low exposed group to compare with. In the present design, confounder control of age tends to give an underestimation of the relative risk of psychoorganic syndrome since age is strongly correlated with cumulative exposure.

Since a clear dose-response relationship could be demonstrated, information-bias is hardly

working to any great extent. Selection-bias is weak according to the study design, and if secondary healthy worker selection is in effect, it has a direction of bias towards the null hypothesis. The most serious threat against the validity of the present study is that of confounding.

The possibility of obtaining valuable information on confounding variables is relatively good in the clinical study where a thorough recall interview can be done and objective examinations carried out. Still two confounding variables are problematic: the primary intellectual level and the question of current solvent exposure, and thereby the possibility of reversibility of the neuropsychological findings. The development of symptoms of mental impairment judged by the anamnesis and the clinical examination is taking into account when evaluating the present intellectual state differing from the prior level. However, only systematic correction is made by the psychometric testing, hereby the use of WAIS vocabulary as a proxy variable for primary intellectual function. Statistical analysis, with adjusted OR < 1 (table 2), indicated that primary intellectual level measured by the WAIS vocabulary were insufficiently adjusted in the final scoring of psychoorganic syndrome.

A little less than 50% of the subjects have not been exposed to solvents within the last month before the examination. Recent TRI-exposure was further expressed by TCA measurements in urine. Forty-one subjects had TCA values in the range of 0,04-26,4 mg/l urine, for 55 subjects no TRI-metabolites were found in urine. The analysis showed that present solvent exposure or exposure within the last month was not associated with the risk of psychoorganic syndrome. Therefore recent solvent exposure cannot explain the findings on effects of chronic solvent exposure.

Some more comments on the evidence of solvent exposure as a cause of chronic brain damage. As described in the introduction, the most consistent results with relative risk estimates of 1,4-3,0 come from 4 pension-register studies in Scandinavia, published in the period 1976-85 and recently confirmed by a US study from 1990 (12, 29, 105, 118, 132). A Dutch and a Swiss pension study both from 1989 and a Norwegian study from 1990 gave low risk estimates or were affected by methodological problems (75, 143, 173). A draw-back in the disability pension studies might be related to the case definition. Subjects with solvent syndrome often manifest themselves with rather diffuse neurasthenic complaints of cerebral dysfunction, which do not fit

well-know psychiatric disorders. The result migth be that these patients do not get confirmed diagnoses, but instead end up on long-term sick-pay or social security money. This would lead to diagnostic differential misclassification and to underestimation of the relative risk.

At the time being the probably most convincing evidence of the causal relation between solvent exposure and organic brain damage is published in a Danish thesis from 1988 (117). A historical cohort of 85 solvent-exposed painters was compared to 85 non-exposed brick-layers. The study population was randomly selected from a union cohort established 6 years before the clinical study was performed - in this way reducing healthy worker selection. Proper confounder control was done and the result was significant odds ratios for painters with medium solvent exposure of 3,6 (1,5-8,5) and for painters with high solvent exposure of 5,0 (2,2-11,4). The main determinants of dementia score were performance in psychometric tests of cognitive impairment. It was also found that dementia score increased with increasing cerebral atrophy. The risk of organic brain damage seemed to increase for accumulated exposure levels above approximately 6 years with a daily time-weighted average exposure of 100 ppm white spirit, which was the main solvent exposure.

In a recent Swedish study from 1995 by Lundberg et al (111), 135 house painters and 71 house carpainters were examined in a pseudo-longitudinal study much like the design of Mikkelsens study from 1988. Neuropsychiatric symptoms compatible with chronic toxic encephalopathy as well as deteriorated psychometric test performance were increasingly prevalent with increasing cumulative exposure - apart from that very sligth effects attributable to solvent exposure were found (111).

In several cross-sectional studies from the last 15 years it has been demonstrated that solvents give rise to high frequencies of neuropsychological complaints and in some degree to reduced psychological test performance (54, 73, 86, 87, 109, 126, 166, 183). These findings were first reported from Scandinavian countries, but in later years also from other Western countries although generally with more inconsistent findings and lower prevalences and odds ratios (24, 61, 83, 113). An explanation behind these differences might be that the Scandinavian study groups are more homogeneous union or factory cohorts, and that selection bias is reduced through high rates of participation. Most studies have an exposure time that in relation to chronic psychoorganic syndrome is borderline low in intensity and duration. Few have exposures as high as in the high exposure group of the present study (11 years of full-time exposure around 60%

the TLV) and that of the painters of Mikkelsen's study (33 years around 40% of the TLV). Another factor of importance may be differences of diagnostic criteria between countries. There is no agreement of a uniform psychometric test battery nor of the clinical evaluation of psychological test performance. A general methodological problem in the cross-sectional studies is the suffering of two kinds of bias, confounding-bias related to inseparability of acute and chronic neurotoxic effects and healthy worker selection -the first one giving rise to overestimation of effect and the second one to dilution of effect.

In other newer studies of different design - historical cohort and register studies - the majority of results show insignificant risks, however, affected by different kinds of selection bias, interpretation of these studies has to be made with caution (42, 97, 129, 138, 169).

8.1.2.1. TRI-exposure and psychoorganic syndrome.

A number of human experiments have been performed where the goal was to measure acute and subacute CNS affection after exposure to high doses of TRI. The exposure range was 33-1022 ppm, and the outcomes were symptoms, and neurologic or psychometric effects (68, 147, 157).

As early as 1931 Stüber described functional neuroses as a part of chronic TRI-intoxication - comparing the state with chronic alcoholism (159). The material was 1 year of referrals of TRI intoxications, 284 subjects, to a Berlin hospital. 113 had a history of acute narcosis with unconsciousness, 25 ended with deaths and in 82 were diagnosed as having chronic intoxication. Since then a number of materials on hospital patients has been reported.

Our primary interest is chronic encephalopathy after long-term exposure in representative groups of workers. In this field the available evidence is restricted to the 11 studies in table 3, where the present study is the only epidemiological study with adjustment for confounding factors (II).

Table 3. Studies of neuropsychological effects after long-term exposure to trichloroethylene.

Profession	Number of exposed/controls	Exposure level	Exposure years mean	Exposure years range	Findings	References
Metal degreasers	50	TRI air: 20-40 ppm	3.8	0.1-15	Chronic toxic encephalopathy 18%. Neurological changes 28%. Autonomic dysfunction 36%	Grandjean et al. 1955 (72)
Dry cleaners	75	U-TCA: 40-80 mg/l	?	0.5-25	Neurastenia 29%, at exposure > 10 years	Bardodej et al. 1956 (19)
Metal workers	104	U-TCA: 20-75 mg/l	1/4> 5 years		Presently exposed: dose response relation of neurastenic symptoms. Previous exposed: No abnormalities	Andersson 1957 (4)
Electronic workers	70	TRI air: 1/6 > 38 ppm U-TCA: 1/4 > 40 mg/l	½ < 2 years, max. 6 years		Pseudo-neurastenic symptoms	Lilis et al. 1969 (102)
Different	130/63	U-TCA: 82% < 60 mg/l	1/3 > 5 years		CNS symptoms	Smith et al. 1970 (152)
Printing workers	30/30	TRI air: 40-160 ppm	3.4	1-5	Neuropsychological symptoms PPR=3-10	El Ghawabi et al. 1973 (55)
Metal degreasers	31/50	TRI air: 20-94 ppm	?	0.1-20	Reduced psychomotor performance	Konietzko 1975 (93)
Printing workers	8	TRI air: 50 ppm	?	?	No abnormalities	Triebig et al. 1977 (167)
Metal workers	188	TRI air: high exp. > 150 ppm	7	?	Neurastenic symptoms. Trigeminal affection	Barret et al. 1984 (21)
Metal workers	100/111	TRI air: 2/3 < 10 ppm	?	?	Neuropsychological symptoms, PPR=3.7 Dose-response relationship	Liu et al. 1988 (107)
Metal degreasers	96	Long-term U-TCA ~ 40-50 mg/l	5.7	0.1-36	Chronic encephalopathy, high exposure OR=11.2 (1.9-66.6)	Rasmussen et al. 1993 (II)

TLV for TRI in air: Denmark 30 ppm (1976-94); since 94: 10 ppm
USA 50 ppm (1990-91).

U-TCA: biological exposure limit in USA = 50 mg/l (30 ppm TRI in air during 4-5 hours corresponds to a U-TCA of 65-85 mg/l).

The first study of an unselected group of TRI-exposed workers is that of Grandjean from 1955 (72). The participants were fifty degreasers from 10 Swiss metal factories, all of whom were still TRI-exposed at the time of investigation. Mean duration of exposure was 3 3/4 years with present air exposure in the range of 20-40 ppm while biological exposure shown by urine TCA ranged from 8 to 444 mg/l, averaging 86,7 mg/l. Neurological changes were found in 28% of the workers. In a psychiatric examination including tests of cognitive function and personality, 17 workers received the diagnosis of slight or moderate psychoorganic syndrome. After exclusion of persons suffering from alcoholic poisoning, or arteriosclerosis or being over 60 years of age, 9 subjects (18%) were allocated to chronic TRI-exposure. Dose-response calculations were done in relation to TRI in air, TCA in urine, and the total length of time spent in contact with TRI, with the most marked dose-response relationship demonstrated associated to the latter parameter. This study of Grandjean is methodologically well-founded. However, sources of limitations include short cumulative exposure time, lack of separability between acute and chronic exposure and incomplete methods of neuropsychological measurements.

Seventy-five dry-cleaners were examined by Bardodej and Vyskocil (19). A symptom-based diagnosis of severe neurasthenic syndrome with anxiety states was found in 1 of 19 persons exposed 2-9 years, and in 7 of 20 exposed more than 10 years.

Andersson reported a clinical study of 140 exposed workers from the metal industry, drycleaning and rubber industry together with a review of 384 cases of intoxication in Sweden from 1941-51 (4). Among 104 currently exposed, a dose-response relationship was demonstrated between signs of neurasthenic disorders and increasing excretion of TCA, but not in relation to duration of exposure. A follow-up of 50 persons who had stopped working with TRI because of different manifestations of intoxication were investigated after more than 1 year of exposure free period. Except for 3 persons with marked fatigue, no persistent symptoms or objective neurological signs were demonstrated. Neuropsychological or psychiatric examinations were not performed.

Lilis et al. examined 70, mostly younger female workers of a semi-conductor manufacturing plant (102). As the duration of exposure for more than half of the group was less than 2 years, and for none did it exceed 6 years, it must be characterized as a study group with low to medium cumulative TRI exposure. After 1-2 years of exposure, "persistent syndromes of the pseudo-neurasthenic type" were described with high prevalences: fatigue 68%, headache 56%, disturbed

sleep 46%, irritability 56%, anxiety 27%, loss of appetite 50%, and alcohol intolerance 21%. These findings are based on symptoms, recorded by questionnaire; no neuropsychological evaluation was performed. Neurological examination showed no significant abnormalities, but 31% had tremors, 34% had hyperactive tendon reflexes, and 7% had nystagmus.

Smith examined 130 TRI-exposed men with a psychometric test battery and compared these with 63 unexposed controls from the same factories (152). A weak dose-response relation was demonstrated between the total length of exposure and neuropsychological complaints combined with evaluation by mental tests.

El Ghawabi was concerned about intoxication after "chronic trichloroethylene exposure" among 30 workers at a print shop where present exposure was very high, with air measurements of TRI between 40 and 160 ppm (55). The cumulated exposure of these workers were however, restricted to a mean of 3.4 years. Comparison was made to 30 non-exposed workers and included registration of symptoms. The conclusion was that of no support for the existence of chronic TRI-poisoning based on clinical examination, electrocardiographic examination and hematological and liver function tests performed. Nonetheless prevalence proportion ratios of acute and subchronic neurotoxicological symptoms were as high as 3-10 with no decrease after 2 weeks off work.

Konietzko presented a battery of motor coordination tests and reaction time to 31 TRI-workers compared to 50 non-exposed control persons and 20 persons exposed to TRI for a short time under laboratory conditions (93). The TRI-workers were currently high-exposed (53% of air measurements exceeded 50 ppm with a duration from 1 week to 20 years. The conclusion was a significant chronic reduced performance level among TRI-exposed workers.

Triebig performed a small study of 8 printing workers who had been exposed 5-8 hours daily at levels averaging 50 ppm (167). Although the purpose was to study psychoorganic syndrome in chronic TRI-exposed persons, the duration of exposure was not stated. Three psychometric tests were given before and after a holiday of 15 days. The test scores were within normal range and did not differ significantly between the 2 test periods.

Barret et al. made a clinical neurological study of 188 machinists, degreasers, and spinners (21).

The subjects were divided in high-exposed (54 persons) and low-exposed by levels of TRI in the atmosphere and TCA in the urine. A symptom picture of asthenia was found among 18,5% of the high-exposed and 4,5% of low-exposed while signs of trigeminal affection was found among 22,2% respectively 7,4% of the 2 exposure groups.

Liu et al. performed a questionnaire study on 103 low to medium TRI exposed and 111 controls (107). Based on a solvent questionnaire with 59 questions the prevalence proportion ratio of a neuropsychological symptom index was 3.7 ($p < 0.01$).

In conclusion it can be stated that the majority of TRI studies on neuropsychological outcome are with severe methodological problems and concerning chronic toxic encephalopathy, diagnostically insufficient. Besides Smith, El Ghawabi, Konietzko and Liu who included some kind of control groups, and Andersson who made af follow-up after cessation of solvent exposure, these studies deal with pure cross-sectional design with presently exposed workers, with no control of confounding factors. The most serious drawback for the question of organic syndrome is probably that the accumulated time of solvent exposure in these studies seems to be too short to give rise to an increased risk of psychoorganic syndrome. Only Barret et al. had high exposure groups at the level of ours and in Barret's study the main stress was on neurological outcome and only symptoms of neurobehavioral toxicity were recorded.

8.1.3. Psychometric tests.

Psychometric methods are sensitive to neurobehavioral disruptions from industrial neurotoxic exposures and are capable of detecting behavioural dysfunction too subtle to be detected by conventional neurological examination (5, 15, 16, 17, 66, 67). But which test items are the most sensitive in neuropsychological assessment of solvent exposed workers and what role does confounding play?

In study III a psychometric test battery of 15 tests with 29 individually scored variables (subtests) was applied. Bivariate analyses of a single psychometric test and the four groups of psychoorganic syndrome no "suspect", "mild", and "mild to moderate" were significant (P-values < 0.01), except for single subtest a motor coordination test of Luria. This result is hardly surprising in the way that these single test performances form a substantial content of the diagnosis of psychoorganic syndrome. More interest should be paid to the relation between solvent expore

and each psychometric test. Linear regression analysis (bivariate results in table 4) showed a significant dose-response relationship between increasing cumulative solvent exposure as a continuous variable from 1 month to 36 years and impaired test performance for 9 of 15 tests (all included in table 4). Further table 4 also shows the result of multiple regression analysis where adjustment for confounding has been made for the 6 covariates used in study II plus word-blindness and the education variable. The strongest association with solvent exposure appeared to exist for the following tests: acoustic motor function, PASAT, and visual gestalts. Significant association at 5% level was found only for the 1st repetition of acoustic motor function and retention of visual gestalts.

Table 4. Multiple regression analysis of psychometric tests which showed significant association between solvent exposure and psychometric test score in linear regression analysis. For comparison bivariate results from the linear regression analysis is shown.

		Intercept	Solvent exposure		Age		Vocabulary		Arterio-sclerotic disease		Education		Word-blindness		Neurologic/ psychiatric disease		Present solvent exposure		R^2
Psychometric tests		β	β	P	β	P	β	P	β	P	β	P	β	P	β	P	β	P	
Vocabulary (h)	Bivariate	56.3	1.7	0.04															
	Multivariate	48.6	0.66	0.42	0.36	<0.001					-6.8	0.01							0.19
Reaction time (l) m.sec.	Bivariate	300.2	8.9	0.04															
	Multivariate	293.5	5.4	0.19					43.0	0.003					33.4	0.03			0.18
Acoustic motor function (h), repetition 1st group	Bivariate	4.0	-0.74	0.0006															
	Multivariate	4.4	-0.47	0.02	-0.13	<0.001	0.34	0.01	1.67	0.01									0.40
Acoustic motor function (h), repetition 3 similar groups	Bivariate	3.4	-0.71	0.001															
	Multivariate	7.3	-0.29	0.14	0.11	<0.001													0.34
PASAT (l) Errors	Bivariate	2.4	0.49	0.10															
	Multivariate	2.0	0.54	0.06									2.3	0.02					0.08
PASAT (l) Time in sec.	Bivariate	58.6	5.0	0.02															
	Multivariate	36.6	2.6	0.23	0.62	0.004													0.14

Table 4 cont.:

Rey A.V.L.T. (h) immediate memory	Bivariate	5.6	-0.28	0.03							
	Multivariate	7.2	-0.10	0.43	-0.05	<0.001					**0.17**
Rey A.V.L.T. (h) learning	Bivariate	12.3	-0.38	0.04							
	Multivariate	10.2	-0.22	0.24	-0.06	0.001	0.36	0.007			**0.18**
Rey A.V.L.T (h) retention	Bivariate	10.2	-0.39	0.14							
	Multivariate	7.8	-0.10	0.69	-.011	<0.001	0.51	0.005			**0.20**
Visual gestalts (l) learning, immediate errors	Bivariate	3.2	0.77	0.001							
	Multivariate	3.0	0.41	0.07	0.11	<0.001	0.31	<0.001			**0.30**
Visual gestalts (l) learning, total errors	Bivariate	4.1	0.91	0.01							
	Multivariate	6.3	0.40	0.26	0.17	<0.001	-0.7	0.005			**0.28**
Visual gestalts (l) retention	Bivariate	3.2	1.3	<0.001							
	Multivariate	8.1	1.10	0.001	1.11	<0.001	-0.7	0.001			**0.29**
Digit symbol (h)	Bivariate	44.1	-2.3	0.02							
	Multivariate	47.2	-0.41	0.64	-0.5	<0.001	1.6	0.02	-6.2	0.04	**0.41**
Revised Santa Ana Dexterity (h) right hand	Bivariate	35.7	-1.3	0.02							
	Multivariate	45.2	-0.06	0.9	0.24	<0.001	-3.3	0.03	2.5	0.02	**0.41**
Revised Santa Ana Dexterity (h), left hand	Bivariate	33.6	-2.1	0.01							
	Multivariate	45.8	-0.75	0.37	-0.34	<0.001					**0.22**
Revised Santa Ana Dexterity (h), both hands	Bivariate	34.5	-2.8	0.002							
	Multivariate	51.0	-1.02	0.24	0.46	<0.001					**0.32**

Table 4 cont.:

Mira (l)	Bivariate	1.42	0.06	0.37			
stairs, right hand	Multivariate	1.08	0.03	0.61	0.46	0.02	0.06
Mira (l)	Bivariate	1.5	0.07	0.31			
stairs, left hand	Multivariate	1.0	0.03	0.62	0.64	0.002	0.11
Mira (l)	Bivariate	1.5	0.13	0.04			
angles	Multivariate	1.18	0.11	0.09	0.40	0.04	0.09

For binary covariates (word-blindness, present solvent exposure, alcohol abuse, arteriosclerotic disease) β refer to the effect if the covariate is present. For continuous covariates β refer to the effect of 10^4 hours of exposure, one year of age and 1 score in vocabulary. The parameter estimate β indicate slope/intercept for solvent exposure and significant covariates.
P=p-value of test for no effect of covariate (β=0).
R^2= variance of the test score explained by covariates in the reduced model.
(h): a high test score indicates good performance.
(l): a low score indicates good performance.

Table 5. Multiple regression analysis of psychometric tests which showed <u>insignificant</u> association between solvent exposure and psychometric test score in linear regression analysis. For comparison bivariate results from the linear regression analysis is shown.

		Intercept	Solvent exposure		Age		Alcohol abuse		Vocabulary		Arterio-sclerotic disease		Education		Word-blindness		Neurologic/ psychiatric disease		Present solvent exposure		R^2
Psychometric tests		β	β	P	β	P	β	P	β	P	β	P	β	P	β	P	β	P	β	P	
Discriminatory attention (h)	Bivariate	6.4	-0.38	0.06																	
	Multivariate	8.1	0.30	0.11									-2.0	<0.001	-1.6	<0.001					0.22
Sentence repetition (h)	Bivariate	6.6	-0.27	0.26																	
	Multivariate	1.3	-0.25	0.23			3.2	0.005	0.58	<0.001			-2.4	<0.001							0.33
Digit span (h) forwards	Bivariate	8.1	-0.21	0.14																	
	Multivariate	9.2	-0.17	0.20									-1.2	0.004	-1.3	0.005					0.19
Digit span (h) backwards	Bivariate	5.7	-0.24	0.11																	
	Multivariate	6.6	0.20	0.17			1.8	0.02					-1.1	0.01	-1.5	0.003					0.23
Text repetition (h)	Bivariate	22.4	-0.62	0.06																	
	Multivariate	14.8	-0.43	0.18	-0.11	<0.001			0.95	<0.001											0.24
Stone picture (l) learning	Bivariate	5.5	0.25	0.33																	
	Multivariate	9.5	0.42	0.10					-0.43	0.01	-2.0	0.01	1.9	0.01							0.17

table 5 cont.

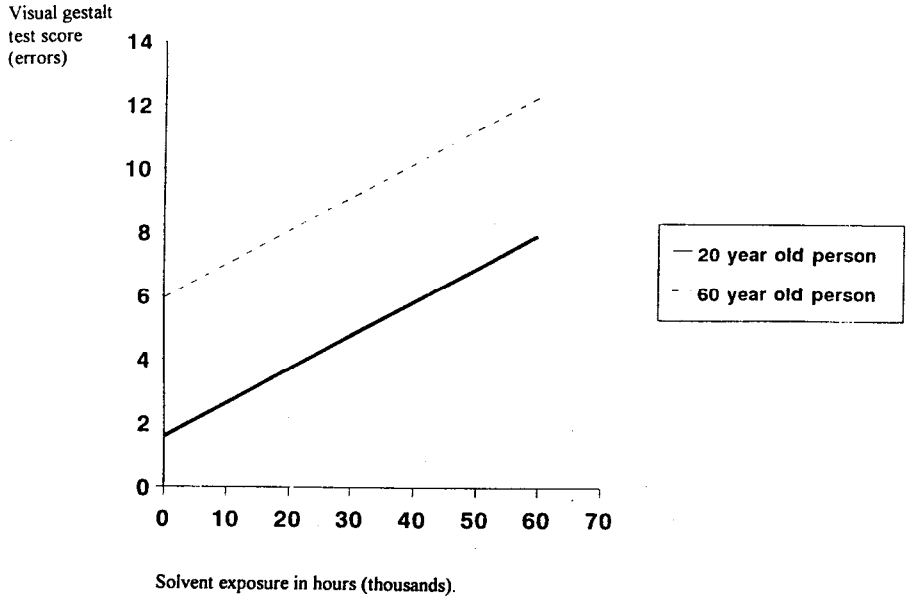
Stone picture (l)	Bivariate	6.8	0.39	0.17							
retention	Multivariate	15.1	0.49	0.08	-0.61	0.002			1.6	0.02	0.15
Luria (l)	Bivariate	1.2	0.05	0.23							
spread/collect fingers	Multivariate	1.0	0.03	0.41			0.26	0.03			0.07
Luria (l)	Bivariate	1.1	0.02	0.74							
fingers vs. 1st finger	Multivariate	1.1	0.02	0.74							0.01
Luria (l)	Bivariate	1.4	0.03	0.74							
Continuous movements	Multivariate	3.0	0.06	0.46	0.13	0.03					0.05

For binary covariates (word-blindness, present solvent exposure, alcohol abuse, arteriosclerotic disease) β refer to the effect if the covariate is present. For continuous covariates β refer to the effect of 10^4 hours of exposure, one year of age and 1 score in vocabulary. The parameter estimate β indicate slope/intercept for solvent exposure and significant covariates.
P=p-value of test for no effect of covariate (β=0).
R^2= variance of the test score explained by covariates in the reduced model.
(h): a high test score indicates good performance.
(l): a low score indicates good performance.

Table 5 contains these psychometric tests which were less sensitive to the effect of solvent exposure. For these six tests or subtests none were significantly associated to solvent exposure, neither after linear nor after multiple regression analysis.

Confounding variables seem to have a very strong influence, substantially reducing the association to solvent exposure. Dominant confounders were primary intellectual function, by the WAIS vocabulary test (significant in 10 of 15 tests), age (in 7 of 15 tests) and education (in 6 of 15 tests). Other confounding variables were arteriosclerotic disease in 4, word-blindness in 3, alcohol in 2, neurological/psychiatric disease in 1, and present solvent exposure which was significant in 1 of 15 tests. Only for the WAIS subtests does a set of age-standardized data exist which is used for age adjustment when these tests are scored in a clinical setting. For all tests, the effect parameter in the analysis in study III are unadjusted raw scores, so it may be expected that age has an important confounding influence. Figure 3 is a visualization of the predicted value from the multiple regression analysis showing the effect of solvent exposure on the visual gestalt retention test, with age as a covariate in 2 different age groups. Exposure to solvents for 60,000 hours (33 years) resulted in a significant increase in errors in the visual gestalt test, the deterioration in performance being equivalent to an increased age of 40 years.

Figure 3. Illustration of the predicted values from selected steps in multiple regression model of test performance, in the visual gestalt retention test in relation to solvent exposure and age.



Discussion.

A major methodological draw-back of study III is the uncertain estimate of the individual prior intellectual function based on the WAIS vocabulary test. This gives an uncertain estimate of whether the present level is acquired or related to primary function. We could have chosen supplementary tests, assumed to be resistent to the effect of organic brain damage, such as Information, also a WAIS subtest. However, the single test most highly correlated to total IQ is the one used in this study, the WAIS vocabulary.

This psychometric test analysis indicated 9 tests as the most sensitive to effects of solvent exposure. Such a result is unlikely by stochastic variation alone. The 9 tests are covering those intellectual functions which according to consensus on "mild toxic encephalopathy" would be anticipated to be positive: psychomotor function, sustained attention and concentration + verbal and non-verbal learning and memory test (18, 181). After adjustment for confounding bias three representing tests of attention and visouspatial function stands as particularly sensitive tests. This is in good accordance with the findings of a Danish house-painter study from 1988 (117).

It is now clear that neuropsychology cannot maintain its former focus on "Localisation, lateralization, and Lesion-detection". Industrial solvent exposure is a particular case in point in relation to diffuse brain damage. There are no focal physical, electro-physiological or radiographic findings after most types of solvent exposure. Thus, neuropsychologists found no markers to localize the effects of these highly lipophilic substances. Three monographs, Lezak, 1983; Hartman, 1988 and Valciukas, 1991, present updated reviews with recommendations for occupational neurotoxicology in line with test procedure and test composition used in this study (81, 100, 170).

A number of human studies from the 60's and 70's reported adverse effects of performance in behavioral tests after acute experimental exposures to TRI (68, 147, 171, 178). Single psychometric tests have also been used to monitor the effects of work-place exposure, including the effect of regulatory procedures (133). During the last decade studies have used these testing instruments in cross-sectional or historical cohort studies of groups of subjects occupationally exposed to solvents through a longer time (47, 61, 88, 117, 176). Study design, analytical approach and main findings in the present study correspond to 2 recent studies with dose-related

neurobehavioral effects in painters and workers from paint manufacturing plants, respectively (24, 155).

We found some psychometric tests more sensitive than others for the purpose of measuring neuropsychological effects of solvent exposure. The results indicated tests of attention and visuo-spatial function as particular sensitive tests. It must be stressed, however, that test performances are only one part of the final assessment of neuropsychological function when the diagnosis of toxic encephalopathy is to be established. Lezak has addressed the issues of emotional deficits and executive capacities, for which no standardized assessment techniques are available, but where an elaborate questioning and clinical evaluation are of importance (101). On the old debate of test battery there now seems to be common agreement on the chore tests included in test batteries used in USA and Europe (81, 170, 181). However, what seems to be an unsolved question is how to make a comprehensible waiting of the cognitive, affective and behavioural components from both the quantitative and the qualitative psychological examination.

8.2. Neurological dysfunction.

In the clinical neurological study (IV) the focus was on cranial nerve disturbances, motor dyscoordination and affection of vibration thresholds. The cranial nerve examination showed a trend to dose-response relation for the olfactory nerve, the sensory function of trigeminal nerve and the sensory function of the facial nerve. The exposure scale was divided into accumulated groups of low, medium and high exposure. In the high exposure group the numbers of metal workers with abnormal function was 4 (9,8%), 4 (9,8%), and 9 (22,0%) for these three cranial nerves, respectively. Only the dysfunction of the olfactory nerve was in trend analysis significantly related to solvent exposure, while this was not the case for the trigeminal nerve, as could be expected according to the literature.

Table 6. The association between solvent exposure and summarized variables of motor dyscoordination and vibration threshold after multiple regression, controlling for the effect of confounders: age, neurological disease, arteriosclerotic disease and alcohol abuse. For comparison bivariate results (linear regression analysis).

	Dyscoordination				Vibration threshold			
	Bivariate		Multivariate		Bivariate		Multivariate	
	β	P	β	P	β	P	β	P
Intercept	0.39		0.43		576.2		290.8	
Solvent exposure	22.6	0.01	24.5	0.01	44.0	0.004	5.0	0.71
Age			-2.7	0.98			8.0	<0.0001
Neurological disease			-0.07	0.84			-23.0	0.63
Arteriosclerotic disease			-0.23	0.49			84.3	0.07
Alcohol abuse			-0.20	0.68			-32.7	0.64

For binary covariates (neurological and arteriosclerotic disease, alcohol abuse) β refers to the effect if the covariate is present. For continuous covariates β refers to the effect of 10^4 hours of solvent exposure and one year of age.

The parameter-estimate β indicates slope/intercept for solvent exposure and covariates.

P=p-value of test of no effect of covariate (β=0).

The performance in motor dyscoordination is presumed to apply to dyscoordination in general, therefore a sum-variable of the 6 coordination tests was created. A significant bivariate trend of dyscoordination from low to high solvent exposure was demonstrated. This association was tested multivariately with 4 confounding variables (table 6) showing that neither age nor neurological disease, arteriosclerotic disease or alcohol abuse had any significant effect. Thus general motor dyscoordination was found associated to long-term solvent exposure where the main solvent was TRI. Two motor coordination tests, Luria motor function and Mira motor function, each with 3 subtests, were performed in connection with the neuropsychological test battery (described above). One of 6 subtests (Mira angles) was significantly associated to solvent exposure in linear regression analysis but after multivariate analysis the association was weak and non-significant for all 6 subtests.

Vibration threshold as a proxy of peripheral neuropathy was recorded at two locations in each of the 4 extremities. At 7 of these 8 points, linear regression showed significant relations between solvent exposure and increased vibration threshold. Also here a sum variable was created and, as demonstrated in table 8, the association vanished after confounding control, with age and arteriosclerotic disease being the dominating covariates.

Discussion.

The shortcomings of the neurological part of the study are substantially the same as described under neuropsychological dysfunction. Alcohol is an important potential confounder variable for the neurological effects. No significant relations were found to the recorded alcohol habits. The reason may be difficulty in getting precise information on the amount of alcohol used, resulting in a false negative effect of the alcohol variable.

Since Plessner's report of trigeminal analgesia in 1915 (134), there have been numerous casuistic publications about TRI as a cause of damage to the central nervous system, in particular with the trigeminal nerve affected (59, 60, 99, 119, 146, 150, 163). After eliminating the problem of soda absorbers in anaesthetic apparatuses using TRI the frequency of trigeminal nerve impairments decreased. Nevertheless, the last decades have brought current reports on multiple cranial nerve affection, some in seemingly average working conditions, and some in extreme exposure situations (20, 114). The end result may be death under such circumstances where autopsy has revealed severe degeneration of structures in the brain stem (36).

Of greater interest from a prophylactic point of view are three newer epidemiologic cross-sectional studies with findings of high prevalences of trigeminal affection using refined neurophysiological methods of examination of TRI-exposed workers. A French study with 188 workers found signs and symptoms of trigeminal impairment in 22% of the high exposure group compared to 7% in the low exposure group (21). In 1987 the same researchers reported the result of a study of 104 TRI-degreasers examined clinically by trigeminal somato-sensory evoked potentials (20). Other values were obtained from 52 healthy non-exposed subjects. Delayed latense time and reduced amplitude were found in 40 of 104 exposed with correlation to exposure gradients. A Dutch study from 1991 of 31 workers with a long term exposure to TRI (20 years at levels around TLV) revealed a prolonged reflectory period of the trigeminal nerve compared to a control group (144).

The result of general motor dyscoordination is in good accordance with findings in a recent Danish investigation of house painters exposed to white spirit and non-exposed brick-layers (117). The odds ratio for general dyscoordination was 2.4 for medium exposure and 5.5 for high exposure painters. Otherwise, solvent studies on dyscoordination are few, unprecisely reported and with unequivocal results. The pattern of the proven dyscoordination indicates that cerebellar and vestibular structures are predominantly impaired. Vestibular dysfunction following acute as well as chronic solvent intoxication has been indicated in a number of studies (7,184).

Vibrotactile measurements may be of diagnostic value in sensory neuropathy. The clinical significance of this, however, is not ruled out. Furthermore a recent study describing a reference population has determined that vibration thresholds are rather age-dependent (25). Two Swedish and one American study of painters have demonstrated increased thresholds of vibration sense perception in relation to solvent exposure (49, 54, 112). Included in these studies are control groups and/or stratified analysis taking into account the effect of age, which must be presumed to be an important confounder. Conventional study methods of peripheral neuropathy with motor and sensory nerve conduction velocity has indicated slight or no effect of TRI as can be seen in two investigations of very relevant study groups of highly exposed persons from the printing and the ceramic industry (144, 165). A Swedish study found slight axonal degeneration in the sensory fibers in subjects with diagnosed chronic toxic encephalopathy and no difference in vibration thresholds among paint industry workers, toxic encephalopathy patients and a reference group (183).

Concerning fluorocarbon exposure, which is relevant for a part of our study, there is slight i.e. casuistic evidence, for peripheral neuropathy (38, 137).

Five solvents have been categorized in a review as "proved human neurotoxicants" (154). One of these were TRI, although not in pure form but through the presence of the decomposition product, dichloracetylene. The criteria to be met were: a consistent pattern of neurological dysfunction in humans, induction in animals under comparable conditions, and neuropathological findings to match. For TRI the damages are sensory loss and motor weakness in the distribution of the trigeminal nerve, transverse myelopathy and brain stem degeneration.

The action mechanisms of cranial neuropathy associated with heavy exposure to TRI are unknown. The most discussed theory has been that a chemical affection is responsible for reactivation of the latent virus of the orofascial herpes simplex (40). In light of the current understanding of herpes simplex infection in nervous tissue this might be an explanation behind cranial nerve damage but it seems unlikely in relation to the generalized cerebral dysfunction of toxic encephalopathy.

8.3. Liver- and nephrotoxicity.

A battery of 6 liver function tests was used to screen for parenchymatous, bile secretory and liver synthetic effects together with a single urine enzyme test to screen for nephrotubular toxicity (V). Table 7 presents the applied tests and dose-response relationships in four groups of increasing solvent exposure. The same scale of cumulative exposure (primarily TRI and CFC 113) as used in the studies II-IV, are here divided into 4 exposure groups with the purpose of creating a wider dose-scale. In the bivariate analysis there seemed to be a dose-relationship for one liver test, the gamma-glutamyltransferase (GGT). The mean value of GGT in the total study group was 30.8 enzyme units/liter, 17 persons exceeded the upper reference limit of 40 u/l. The range of GGT values for the 17 subjects were 45-183. However, multiple regression analysis showed alcohol abuse and age to be strong confounders and a significant relationship could not be demonstrated between degreasing solvents and GGT after adjustment for age and alcohol (table 8).

Table 7. Mean levels of liver and kidney tests by 4 groups of increasing cumulative solvent exposure.

	Exposure groups*				Linear regression	
	I (N=23)	II (N=25)	III (N=26)	IV (N=26)	Slope	P-value
S-ASAT µ/l	21.3	23.6	20.5	22.2	0.1	0.91
S-GGT µ/l	16.2	32.4	26.7	44.6	-6.3	0.03
S-alkaline phosphatase µ/l	162.5	158.8	148.2	157.2	1.7	0.61
S-bilirubin µmol/l	8.6	7.8	9.0	7.5	-0.1	0.68
S-protein g/l	71.0	70.9	69.7	70.1	-0.4	0.29
P-prothrombin u/l	94.9	98.2	97.0	94.8	-1.3	0.53
U-NAG u/g creatinine	42.7	51.4	51.8	65.1	6.2	0.05

* Number of years of full-time exposure:

	mean	range
gr. I:	0.6	0-0.99
gr. II:	1.9	1-2.8
gr. III:	4.4	2.9-6.7
gr. IV:	14.4	6.8-35.6

\+ Linear regression analysis (calculation of deviation of mean values from horizontal slope refers to the effect of 10^4 hours of cumulative solvent exposure). The linear regression was made on continuous exposure and effect variables.

Table 8. Multiple regression analysis of the two tests with significant bivariate association to cumulative solvent exposure, serum gamma-glutamyltransferase (S-GGT), and urinary NAG activity (U-NAG).

	S - GGT				U - NAG			
	Bivariate		Multivariate		Bivariate		Multivariate	
	β	P	β	P	β	P	β	P
Intercept	24.8		4.4		47.0		40.6	
Solvent exposure	-6.3	0.03	-4.6	0.13	6.2	0.05	5.4	0.11
Age			0.5	0.08			0.18	0.61
Alcohol abuse			27.7	0.07				

The parameter estimate β indicates slope/intercept for solvent exposure and covariates.
P = p-value of test for no effect of covariate (β=0).
For the two continuous covariates, β refers to the effect of 10^4 hours of solvent exposure and one year of age.

A similar course was the result of the analysis of the urinary NAG activity as an indicator of urinary tubular injury. An association, significant at 5% level, was found in linear regression (table 8). This result turned into non-significance after multiple regression with age as the single covariate (table 8). We carried on the analysis concerning NAG by testing the association between present exposure to TRI and present exposure to all organic solvents. The result was insignificant signs of acute effects. In screening for renal glomerular function we found two subjects with proteinuria after a qualitative sticks-method and none with erytrocyturia.

It should be observed that 8 persons revealed NAG values higher than 100 units (range 102-194) - from diabetic patients 100 units are taken to be a limit indicating subclinical neuropathy. Repeated sampling half a year later of these 8 high-NAG-workers showed that 5 of 8 still had signs of persistent kidney affection (33).

In conclusion study V showed that long-term exposure to the degreasing solvents TRI and CFC 113 was not statistically significantly associated with a battery of liver function tests and one renal tubular test.

Discussion.

Abnormal liver function tests and liver biopsy showing steatosis, has been demonstrated after acute intoxicative exposure to TRI, 1,1,1-trichloroethane, CFC 113 and toluene (76, 80, 108, 160). Occupational epidemiological studies of workers with mixed solvent exposure show unequivocal results (51, 94).

Our finding indicating GGT to be a sensitive parameter of liver screening has been confirmed by a recent study from Taiwan of xylene and toluene exposed workers from paint-manufacturing and spray-painting factories (41). This study included proper confounding control for the non-occupational factors: alcohol, medication, age, and hepatitis B viral infection. The results showed that GGT activity was associated with both exposure and the consumption of alcohol. A Japanese investigation from 1993 of degreasers exposed to medium levels of TRI included a cross-sectional as well as a follow-up study (123). The conclusion was that TRI exposure influences epatic functions, affecting cholesterol metabolism rather than causing epatic damage measured by a SATT ALAT and GGT, and that these effects are subclinical and reversible.

Other newer studies have suggested the determination of plasma bile acids as the most sensitive

indicators of changes in hepatic function (50, 63, 64, 110). In an Australian study from 1992 the bile acid concentration was measured in 2 groups of workers, TRI-exposed degreasers and workers from a solvent production plant with exposure to a mixture of chlorinated solvents including hexachlorobutadiene (50). The findings were highly significant increasings in a range of plasma bile acid measures in workers exposed to TRI and a dose-dependent increase in concentrations of some serum bile acids with increased exposure to hexachlorobutadiene. The effect of age and alcohol intake was confirmed by confounding analysis. There were no associated changes in common liver function tests.

A number of case-control and cohort studies together with animal experimental evidence is the basis for considering autoimmune glomerulo-nephritis as the most conclusive relationship between solvent exposure and clinical renal disease (135, 142). Subclinical renal damage is thougth to be best surveyed by measuring urinary enzymes as an indicator of loss of tubular epithelial cells (22, 62, 136, 156, 172). Urinary NAG activity seems to be one of the most applicable enzyme parameters (98, 115, 182). We were not able to identify any TRI-studies using NAG in screening for renal affection. However, NAG was the parameter of measurement in the investigation of Solet et al. from 1991 concerning perchloroethylene exposed drycleaners (153). No consistent relationship to acute and chronic exposure variables could be demonstrated; NAG was weakly but insignificantly associated to age. Nagaya et al. found insignificant increases in urinary total proteine and β-2-microglobulin among TRI-exposed workers compared to a control group; no proper confounder control was made in this study (122).

8.4. Genotoxicity.

The genotoxic examinations in study VI were performed only in a high exposure group. The criteria of inclusion were present full-time degreasing with TRI for more than 20 hours per week. This was the case for 8 full-time degreasers (40 hours/week) and 7 part-time degreasers (20 hours/week). The mean urine TCA was 3.7 mg/l (range 0.2-26.9) for the 15 workers, while the cumulative exposure calculated in full working years with TRI was 4.6 years (range 0,8-22,0). Semen analysis of common quality parameters: sperm count, volume, motility, and morphology showed no marked differences between TRI-exposed persons and a control group of non-exposed medical doctors. Two fluoroscent bodies (YFF%) may indicate a chemically induced presence of two Y-chromosomes. Table 9 shows an increased frequency of YFF% in the TRI-exposure group, a difference that was statistically non-significant.

Table 9. YF and YFF frequencies in sperm cells in exposed and control group.

	Sperm cells analysed n	YFF cells n	YF% Mean	YF% 95% confidence interval	YFF%[a] Mean	YFF%[a] 95% confidence interval
Exposed group (n=12)	7472	126	45.2	(43.7-46.8)	1.7	(1.4-2.0)
Control group (n=14)	7396	103	44.8	(43.3-46.3)	1.4	(1.1-1.7)
P-value[b]			>0.10		>0.10	

[a] $\frac{YFF}{XX \times XY} \times 100$

[b] Mann-Whitney Rang-sum test

Table 10. Unstable chromosomal aberrations in lymphocytes in exposed and control group.

	Exposed group (n=15) Mean (%)	Exposed group (n=15) 95% confidence interval	Control group (n=669) Mean (%)	Control group (n=669) 95% confidence interval	p-value[a]
Number of metaphases analysed	1261		7889		
Gaps	21.66	(19.17-24.40)	2.80	(2.44-3.20)	<0.001
Breaks	1.90	(1.22-2.84)	0.85	(0.66-1.08)	<0.001
Sum of translocations, deletions and inversions	1.35	(0.79-2.16)	0.15	(0.08-0.27)	<0.001
Hyperdipliod cells	0.79	(0.38-1.46)	0.24	(0.15-0.38)	0.0013

[a] χ^2-test

Table 10 shows frequencies of unstable chromosome aberrations in cultured lymphocytes. The result was highly significant increased frequencies in the exposed groups, especially concerning gaps and a sum-variable of pronounced aberrations: translocations, deletions, and inversions. A second control group was used for this comparison, consisting of subjects sampled for cytogenetic population studies. Unfortunately, information on confounding variables was not available for this reference group.

Initial confounding analysis was performed by examining the distribution of the following variables: high alcohol consumption and events through the last 3 months of febrilia, viral disease or X-ray examination. These potential confounding variables were in bivariate analyses found distributed with no correlation to the effect measures. Still the weaknesses of this study are related to a lack of proper confounding control, and the restricted study population.

An attempt to dose-response analysis was done by investigating the distribution of outcome after dichotomizing the group in full and part time degreasers. Those working full-time with TRI seemed to produce more chromosomal gaps and breaks and more abnormal heads of spermatozoa. Furthermore, looking at coherence of the material we found the highest proportional Y-chromosomal non-disjunction and abnormal heads in the groups with most chromosomal aberrations.

Discussion.

Throughout the last decade, studies have indicated that lead, vinyl chloride, dibromochloropropane (DBCP) and cytostatic agents may affect sperm cell formation and induce chromosome aberrations (39, 69, 96, 82, 90, 128). Epidemiological studies on reproductive outcome of paternal exposure to hydrocarbons have been inconclusive (23, 158). Four other studies of cytogenecity after occupational TRI-exposure have been published (74, 92, 124, 149). Two older studies have small sample sizes and incomplete control of confounding bias (74, 92). Konietzko et al. found an increased number of hypodiploid cells in cultured lymphocytes correlated to high TRI-exposure with pathological rates of hypodiploid cells in 9 of 28 degreasers (92). Further they found structural chromosome aberrations in 3% of analysed metaphases compared to 0,6% among the controls. A small French study of 6 TRI-degreasers demonstrated significantly increased rates of sister chromatid exchange in comparison to 9 unexposed (74). The present exposure was high, but further information on exposure variables and the relevant covariates was

poor. In two newer Japanese studies there were found either no or weakly increased frequencies of sister chromatid exchange in relation to TRI-exposure (124, 149). In the study of Nagaya et al. with 22 highly-exposed to TRI (30 ppm), there was no association to TRI but a weak association to smoking (124). Seiji et al. examined 38 low-exposed to TRI (7 ppm) (149). Here the findings were a weak but insignificant increased frequency of sister chromatid exchange related to TRI, none to smoking as a separate variable, although the most marked and significant effect with $p < 0,01$ was found when exposure to both TRI and cigarette smoking were present, indicating synergestic action.

The effect of smoking on chromosome aberrations, sister chromatid exchange and oncoprotein was explicitly the object of a study of 20 smokers and 20 non-smokers not otherwise exposed to any specific chemical hazard (32). No effect was found on any of these endpoints with the exception of a moderate, statistically non-significant elevation of the sister chromatid exchange level. It was concluded that smoking is unlikely to be a confounding factor in human monitoring studies using these cytogenic parameters.

TRI is one of the most frequently tested organic solvents in short-term mutation tests. In a recent review from 1991 Skogstad and Kristensen summarize the result of TRI tested in 33 in vitro mutagene systems with a positive outcome in 22 (151). An unsolved question is whether the presence of epoxicides and anti-oxidant stabilisers in TRI are the actual causative agents. In 10 animal in vivo mutagene tests TRI was demonstrated as positive in 5 (151).

Since the National Cancer Institute of USA in 1976 reported hepatocellular carcinomas in TRI-fed mice, several animal experiments have confirmed TRI as a species-related carcinogen of some potency (151). Coming to epidemiological studies, evidence of TRI as a human carcinogen is scattered, pointing at TRI as at the most, a weak carcinogen (13,185). Since Axelsson et al. extended their TRI-cohort, they found significant excess mortality of cancer in the urinary tract and the haematopoetic system (13, 14).

A recent review summarizes the evidence from the 4 most solid cohort studies (185) The findings were weakly increased risks of cancers of the liver and biliary, tract and for non-Hodgkin lymphona.

Case-control studies have been with either few cases or few TRI-exposed cases (65, 79). Frederiksson et al. found that the risk of colon cancer was increased among TRI-exposed

drycleaners with an OR of 7.4 (1.1-47.0) (65).

The carcinogenic potential of TRI is still uncertain. However it would seem that there is sufficient evidence to conclude that low-grade exposure to TRI is not a serious cancer hazard. According to current IARC guidelines TRI is classified as being probably carcinogenic to humans.

8.5. General health assessment.

At the time of the clinical examination 81 workers were employed, 9 were unemployed, and 4 were on sick leave (3 because of common respiratory tract infections and 1 subject because of chronic headache). Finally 5 had retired - 4 because of age, and 1 because of illness with a diffuse disease picture, where chronic toxic encephalopathy of mild to moderate degree was the only clarified diagnosis. Pulmonary function was tested using a dry spirometer giving values of 8 basic lung function parameters - individual predicted values were calculated by the spirometer based on age and height. No pulmonary findings of health significance were recorded aside from 1 subject with an earlier confirmed asthma of non-occupational origin.

Mean and range of diastolic blood pressure was 79.6 (60-110) mmHg and of systolic blood pressure, 127.3 (105-180) mmHg.

By electrocardiography in 9 leads we found 1 with left-sided cardiac hypertrophia, 4 subjects with incomplete, 2 with complete branch block, 2 with myocardial ischaemia and 2 with former myocardial infarction. These last-mentioned six persons were included in the confounder variable arteriosclerotic disease.

Both TRI and CFC 113 are known for cardiac toxicity, especially their ability to cause cardiac sensitization and arrythmias. This has been demonstrated in human experimental as well as occupational observational studies (102). These findings should have been followed up through continuous monitoring during the work shift rather than by stationary ECG-measurements as done here. We found no ECG changes that were related to TRI exposure.

9.0. Conclusions and perspectives of the health study.

A main issue of these studies has been chronic brain damage after long-term solvent exposure. The causal linkage was studied in the framework of dose-response relationships. The risk of developing psychoorganic syndrome was proportional to the duration of exposure to increasing age and to decreasing primary intellectual level. Using logistic regression analysis there was a significantly increased risk of having psychoorganic syndrome in the high exposure group with a mean full-time exposure duration of 11 years (range 4,0-35,6 years) - OR = 11,2 (1,9-66,6). TRI was a dominating solvent exposure. Throughout the 60's and 70's there is by this study indication of TRI exposure levels of around 2/3 of the TLV of 30 ppm, from the late 70's exposure levels have declined in Denmark as well as in many other industrialized countries. The inclusion of a study group of sufficiently long term and highly exposed workers is crucial to the findings of chronic toxic encephalopathy in this and a few other methodologically well-founded newer studies, compared to the negative or inconclusive results from studies using groups with substantially shorter duration of cumulative exposure. That the metal degreasers actually have been exposed to substantial levels of solvents is not as in most studies exclusively based on occupational interview data, but also on historical register data of biological monitoring. Although these historical data are encumbered with insufficiences as they are not correlated systematically or representatively among Danish workers exposed to TRI, they represent with 1544 measurements over 41 years the best historical data of solvent exposure in Denmark - better than what is available for other solvents. Levels and trends in our study VII correspond to those of a similar but smaller survey of historical U-TCA data from the Swedish National Institute of Occupational Health (103).

What is the state-of-the-art concerning solvent exposure and dementia? From 1976-1990 there have been published 8 register-based pension studies with significant association between solvent exposure and neuropsychiatric disorder in 5 of 8 studies and insignificant risk estimates or considerable methodological drawback in 3 studies (12, 29, 75, 105, 118, 132, 143, 173). Supportive evidence comes from the 1988 study of a historical cohort of Danish house-painters and bricklayers and the present cohort study of TRI degreasers (117, II). The vast number of cross-sectional studies reported from many countries suffers from potential bias of healthy worker selection and confusion of acute and chronic effects leading to underestimation and overestimation respectively of demential findings. However, a single cross-sectional study,

exactly on TRI exposure, deserves attention because of some other advantages. The Swiss study of Grandjean et al. from 1955 is comparable to the present one in terms of study sampling, effect parameters and analytical approach (72). The Swiss study was a cross-sectional study on 50 subjects from 10 metal plants. Ours included 99 subjects from 49 plants in a cohort design partly taking into account the effect of confounders. The exposure seems to have been at the same level but the cumulated exposure was only half as high in the Swiss study. A dose-response relationship between TRI exposure and psychoorganic syndrome was demonstrated in both studies, although diagnostic criteria are not identical. No other occupational TRI-studies give firm evidence to the question of chronic brain damage.

As psychometric tests serve an important diagnostic role in the neurotoxicological studies, the consequence of confounding of these testing instruments has to be elucidated. The most sensitive tests to the effects of diffuse organic brain damage was acoustic motor function and PASAT (attention tests) and visual gestalts (a learning and memory test). We found the dominant confounders to be primary intellectual function, age and education. There is a need for international agreement on a psychometric core test battery with normative data as well as on diagnostic criteria on psychoorganic syndrome. Future solvent studies should be follow-up studies. Of importance are detailed data for long-term exposure assessment and more precise information on premorbid function, e.g. through the use of previous psychological military test scores, or better, more goal-directed primary psychological data (10).

The main finding in the clinical neurological study (IV) was a highly significant dose-response relationship between solvent exposure and clinical neurological signs of dyscoordination. Manifest outcomes from the trigeminal nerve and also from multiple cranial nerves has previously been related to TRI. Probably this is the result of either accidental peak exposure or long-term high exposure. In our group of long-term medium exposed we found disturbances from cranial nerves no. I, V and VII with a significant relationship at bivariate level for only the olfactory nerve. By clinical neurological examination no signs of polyneuropathy was demonstrated. Vibration thresholds as an indicator of peripheral nerve affection increased with solvent exposure, but insignificantly since multiple regression analysis revealed age as a dominating explaining variable. This is in accordance with the literature, from which it can be inferred that peripheral nerve impairment caused by TRI is less frequent and less severe than that occurring after N-hexane exposure, the solvent primarily related to polyneuropathy.

Some chlorinated hydrocarbons as carbontetrachloride are known to be potent hepato- and nephrotoxic chemicals. It is still broadly thought that chlorinated solvents are more toxic to the liver and kidney than non-chlorinated solvents. It is however, an unsolved controversy whether this is the case under the low exposures present at modern work-places. Under such circumstances, the hepato- and nephrotoxic potential seems weak or of doubtful health significance. We found a trend to dose-response relationship between long-term exposure to solvents, mainly TRI and GGT, testing liver function and NAG, testing renal tubular function. After confounding control, the association was insignificant. Future studies should include aspects of acute and chronic exposure (retired workers), both liver function and bile acid parameters and, concerning renal function, a battery of tubular enzymes.

In study VI we found correlation between TRI exposure and mutagenic effects, with the main findings being somatic chromosome aberrations. In this study, the only one reported including germ cell parameters of TRI-exposed subjects, an increase in YFF% (a proxy for presence of 2 Y-chromosomes in spermatozoa) was small and insignificant. Until now 5 studies have been published of cytogenetic changes among occupationally TRI-exposed. Two studies on chromosome aberrations were positive. One of three studies with sister chromatide exchange as effect parameter was positive, one among highly-exposed was negative, and 1 with low-exposed workers was inconclusive. On the basis of this evidence and short term mutation tests, it seems justified to consider TRI as a mutagene of medium potency. How should this knowledge be interpreted in terms of health consequences? Most important is the teratogenic questions. With present knowledge, pregnant women should not be occupationally exposed to TRI, unless in circumstances of very low exposure. In terms of cancer risk there is quite a body of human and animal studies. Results are conflicting, but nevertheless indicate at the most a weak human carcinogen. In view of the serious consequences and difficulties of taking firm preventive actions on present knowledge, the carcinogenic and genotoxic effects of TRI-exposure should be a field of further research. The lack of knowledge regarding the incidence of molecular markers as chromosome damage in normal populations is a serious drawback to their use as monitoring instruments.

It has long been recognized that the primary target organ for solvents is the nervous system. This is also the case for TRI and other chlorinated solvents, although a broader profile of effects has been demonstrated in this study. What should be the consequences in terms of occupational

hygiene based on this study and other existing knowledge? The level of TRI exposure in the present study is anticipated to be at air concentrations around 20 ppm from the 60's and 20-25 years ahead. Working conditions creating such exposure levels probably still exist in many industrialized as well as developing countries. Relevant precautions should be taken against exposure to TRI including work-hygienic procedures and continuous health surveillance by monitoring of U-TCE of exposed workers. With its great distribution and technical efficiency TRI will remain a dominating degreasing agent for decades ahead. Based on the total evidence of solvent toxicity the Danish TLV of TRI has from January 1, 1994 been lowered from 30 ppm to 10 ppm.

The historical exposure data of this study (VII) with a degreasing trend of exposure since the mid-70's give support to a view that we to some degree in these years are studying things of the past. On the other hand the use of organic solvents is now distributed to a lot more trades than in the 50's and 60's. From a survey performed in 1985 at The Danish National Institute of Occupational Health it is assumed that every second person employed in manufacturing industry, construction, health care, service and repair in Denmark, frequently or daily encounters organic solvents in their work (131). Although chlorinated solvents for degreasing gradually become substituted by water-based alcalic agents, this process runs slowly. In a referred Danish survey from 1985 particularly chlorinated solvents from many chemical cleaning and degreasing purposes gave rise to the most frequent and large exceding of threshold limit values - exceedings of 6-10 times of the TLV (131). So health effects after exposure to organic solvents are hardly not a thing of the past in the story-writing of occupational medicine.

10.0. Brain damage resulting from solvent exposure: etablishing scientific evidence and social recognition.

10.1. Early history.

The first systematically collected medical descriptions of chronic solvent poisoning were undertaken by the French physician, Auguste-Louis Delpech, in 1856-63 (130). One had for some time at this point utilised carbon disulphide as a solvent in the process of vulcanizing rubber; rubber was manually dipped into large open baths filled with fluid CS_2. It was also used at this time in the treatment of different diseases, as both a local and general anaesthetic, and as a solvent during the production of medicine. These areas of application are very similar to those we see for TRI, some 80 years later. On the 15th January 1856, professor Delpech held a lecture at the French Academie de Médicine, in which he characterised the psychological symptoms that he had observed in workers employed for a few (3-5) years at the Parisian rubber factories. These symptoms were described as: "impaired intellect, reduced memory, vague and confused thinking. Alternation between foolish cheerfulness and violent temper, sleeplessness, mental unrest, unpleasant dreams and sudden nocturnal waking. During the day, drowsiness, despondency, apathy and inactivity". Patients experienced constant headache, dizziness, impotence, paralysis of the extremities and muscular atrophy, extensive loss of feeling, etc.. Over the next 7 years, Delpech assembled material on 23 poisoned individuals, both men, women and children, which was presented in journals and a comprehensive monograph. Delpech's reports showed that long term exposure to carbon sulphide left these persons chronically disabled and in a state of considerable memory loss.

After the first world war, the mass production of automobiles at Ford car factories in the USA came underway. Lacquering created a bottleneck, since the oil paints used required 1-2 days to dry, and a complete paint job took over a week. Fast-drying cellulose lacquers and a new application method with paint-guns were therefore developed. Shortly afterwards, Danish carriage painters adopted the same type of cellulose lacquer. There soon appeared hitherto unknown toxic complaints from painters, and to such an extent that medical investigations were implemented. In the USA the state of Pennsylvania took the initiative, while in Denmark, it was taken by doctors at St. Hans Psychiatric Hospital, who were perplexed by the case of a young painter with symptoms of intoxication and a mental breakdown. This was the start of the first Danish investigation, an interview-based study of 73 carriage painters, which was published in

'Hospitalstidende' in 1933 (53). This report describes not least complaints of personality changes such as irritability and seediness, symptoms taken to be signs of chronic poisoning. These symptoms disappeared however, in connection with holidays, in half the cases.

Cases of poisoning following work with chlorinated solvents appear for the first time in German journals. Plesner's case study descriptions of affected cranial nerve functions in TRI-exposed metal degreasers were published in 1915 (134). The next example is Stüber's (1931) examination of 284 patients, who constituted all cases of TRI-intoxication referred to a single Berlin hospital during a 1-year period (159). Clearly the phenomenon was not rare. The first Scandinavian material concerning chlorinated hydrocarbons appears in 1938 in Nordisk Medicinsk Tidsskrift (Nordic Medical Journal), and describes 9 cases of TRI-exposed laundry workers from Oslo (148).

Poul Bonnevie, who was professor of hygiene and social medicine at the University of Copenhagen from 1948-77, and an occupational physician with The Working Environment Service and, periodically, the Department of Occupational Medicine at Rigshospitalet (National Hospital of Denmark), has played a special role in Denmark regarding the early and continuing provision of information on acute and chronic solvent poisoning. He observed many cases personally and instigated their closer examination by travelling throughout the country and visiting dry-cleaners, metal works, and painting workshops. He drew attention to solvent poisoning as early as in 1939 at the annual meeting of the Working Environment Service. His warnings appear in written form for the first time in 1943 in a book on worker protection (70). Here he writes: "Permanent changes in emotionality, ranging from irritability to actual psychiatric disorders may be observed in spray-painters, and is without doubt a sign of lasting brain damage. In consideration of the relatively short time span, no more than 10 years, in which greater exposure to the newer solvents has occurred, it is necessary to take into account the possibility that long-term effects in other organs will appear, as is the case with chronic carbon sulphide and alcohol poisoning".

From 1951, Bonnevie includes a chapter on organic solvents in his textbook on hygiene. This mainly concerned classification (into group A solvents, which were the most dangerous, e.g. chlorinated solvents, and the less toxic group B solvents), but also a little scattered information about symptoms (28). This publication, and its subsequent revised editions, was the prevailing

textbook on the field of hygiene and social medicine, which at this time included occupational medicine, used at Danish medical faculties until the late 1970's. In the first edition from 1951, Bonnevie writes; "The gradual chronic poisoning produced by 'TRI' often manifests itself in psychological symptoms with emotional and personality changes. A long recuperation period is necessary, often as much as a couple of years". Bonnevie also draws attention to the problem in a case study, published in 1952 in Ugeskrift for Læger (The Danish Medical Journal) (27). This discusses a 27-year-old worker employed with the cleaning of aeroplane motors with TRI: "There can be long-term emotional and personality changes with a neurotic or psychotic character".

A quite remarkable study, judged by present methodological standards, was published in 1955 by Etienne Grandjean et al, from the Institute of Hygiene and Industrial Psychology in Zurich (72). This was the first investigation that can be characterised as an epidemiological study and encompassed all workers using TRI-degreasing agents at 10 metal works. The study was published in the respected British Journal of Industrial Medicine. Out of 50 workers who underwent neurological and psychological examination, 9 were diagnosed as having chronic psycho-organic syndrome following TRI-exposure. Throughout the present century, descriptions of toxic reactions to solvents have appeared in both Danish and international medical journals. These have usually been based on case study material, covering both acute neurotoxic symptoms and chronic symptoms of psychotic-like behavioural disturbances. The term chronic appears mainly to have been used to mean long-term rather than irreversible. A well-defined description of a chronic, cerebral solvent syndrome does not yet exist. Furthermore, the texts and articles mentioned here have, on the whole, been sporadic, and it is unlikely that they have reached doctors and authorities with a clear and consistent, let alone documented message.

10.2. From casuistic to scientific clarification, 1976-1995.

From the mid-1950's and for 20 years thereafter, relatively little is heard concerning the health effects of solvents. New studies do not appear in the literature. However, in 1971, the Finnish occupational psychologist, Helena Hänninen, published her pioneering work on chronic, neuropsychological manifestations in workers exposed to carbon disulphide during the manufacture of synthetic fibres (88). This was a rediscovery of Delpech's findings 110 years earlier, this time however, founded on a solid study design and the use of diagnostic, neuropsychological tests. There followed yet another Finnish study (Lindstrøm, 1973), in which

a group of 42 persons, referred for clinical examination for solvent poisoning, were found to exhibit reduced performance on psychological tests in comparison with a non-exposed control group (104). A further group of subjects, with verified CO_2 poisoning, were also employed for comparison purposes and found to function even worse on these tests.

It is not until the last half of the 1970's though that one really begins to focus on solvent syndrome. It starts with Finnish and Swedish studies of construction painters in 1975-76 (77, 87). In Denmark, Lou and Stockholm (1976) present a case study of solvent syndrome in a construction painter. Lajer (1976) presents a simple interview-based account of the frequency of mucous membrane and neurological complaints in 38 construction painters, all of whom had an acute exposure, compared with a similar number of electricians (95). More studies follow in 1978 and 1979 in Denmark and the rest of Scandinavia, focussing on printers, carpenters, construction painters, spray-painters from the car industry and workers from the paint manufacturing industry (9, 55, 73, 86, 145). These investigations use questionnaires or diagnostic psychological testing and include persons who are still in work and exposed. A further 3 studies between 1976 and 1980 show an elevated risk of early retirement due to neuropsychological causes amongst painters and carpenters. These studies have been mentioned earlier in this review (12, 118, 132).

Thus, the period from 1976 to 1980 saw quite a large number of medical studies from the Scandinavian countries. Methodological problems exist regarding diagnostics, a lack of or insufficient control groups and a lack of separation of acute and chronic symptoms. The conclusions in these articles are accordant however, pointing to an increased frequency of complaints such as headaches, dizziness, tiredness and difficulties with concentration and memory amongst solvent exposed individuals, who were most often painters. Painters' syndrome was thus characterized.

International studies of painters, e.g. from Germany and the USA, also appear in the late 1970's and early 1980's with essentially the same conclusions as those undertaken in Scandinavia. A number of international studies, though, are unable to confirm the Scandinavian results (61, 113, 165). As a result of methodological discussions, new, more solidly designed studies are undertaken. Sigurd Mikkelsen's historic cohort study of painters, with bricklayers as a control group, was published in 1988 (117). The present study of metalworkers was published in 1993-94. A breakthrough in the scientific debate and recognition of solvent syndrome occurs in 1985.

The first international conference on the subject is held in this year in Stockholm. Much debate takes place and scepticism is aired, many questions remain unresolved; consensus is not achieved at conferences. An attempt to reach a consensus was, however, the goal of a gathering of selected researchers from Europe and the USA under the auspices of WHO, likewise in 1985. This meeting resulted in the official recognition of chronic solvent syndrome, as well as the creation of diagnostic categories and to a certain extent, diagnostic criteria (181).

During the first half of the 1990's, several new international studies have appeared, especially from the USA (24, 29). They employ the same designs and study populations as the Scandinavian studies and do not provide much in the way of new knowledge. As a whole, there now exists reasonable international agreement that exposure to levels of organic solvents, that were normal in western industrialised countries in the 1960's and 1970's, has caused an increased risk for lasting damage to the functional cerebral status of workers with a high cumulative exposure, and that this exposure has caused an increased risk of early retirement on the grounds of neuropsychological disease (85). That, which for a while was sarcastically referred to as "The Scandinavian Solvent Syndrome", now enjoys scientific recognition. Exposure duration and diagnostic conditions, however, remain as partly unresolved questions.

When evaluating the probability of a relationship between exposure to organic solvents and toxic encephalopathy, the conventional epidemiological principle that a single study does not provide a sufficient basis for conclusions applies. The current level of knowledge is an overall evaluation of existing research findings. The earliest studies of solvent syndrome were purely descriptive case studies or studies based on selected groups of patients, so called "case-only-studies", which provided a picture of the clinical elements of toxic encephalopathy. Cross-sectional studies using various control groups subsequently provided the possibility of calculating prevalence proportions of the syndrome, which by now had begun to emerge. Case control and cohort studies then led to risk estimations for the syndrome.

A particular date for the attainment of a consensus about chronic solvent syndrome cannot be identified. In Denmark, this consensus was arrived at gradually in the years 1976-85. Internationally, the breakthrough came in 1985, even though the best studies first appeared 3-8 years later. The optimal study design has never been adopted, and is unlikely to be so. This would entail clinical baseline studies of non-exposed individuals and reexamination 15-30 years later,

after the exposure of some subjects to solvents and the continued non-exposure of control subjects. Further design requirements would be to control for intellectual and psychological capacity prior to exposure, precise estimates of exposure during the study period, and uniform, observer-blinded medical and psychological examinations. In many western countries, and certainly in Scandinavia, workplace exposure levels have fallen during the last 10 years to a level that make such a study irrelevant. Exposure levels that are high enough to make such a study relevant do exist, for example, in the timber and furniture industries of the emerging industrial countries of south east Asia. But considering the reasonably well documented knowledge we now have about solvent conditioned brain damage, such a study design can hardly be implemented for ethical reasons.

10.3. Acknowledgment by the National Board of Industrial Injuries.

The National Board of Industrial Injuries officially recognised the first cases of painters' syndrome, i.e. chronic toxic encephalopathy, as an occupational disease for which workers could receive compensation in 1976. In the same year, the first cases were recognised by the equivalent Swedish compensation system. It was also in 1976 that the first articles concerning solvent syndrome appeared in national Danish and Swedish medical journals. Prior to 1976 there had been just a few accepted cases of *acute* poisoning following work with solvents. Table 11 depicts the number of cases recognised by The National Board of Industrial Injuries from 1976 to 1994. As can be seen, there were relatively few instances in the first years, and all of them entailed separate evaluation by The National Board of Industrial Injuries with the involvement of consultant specialists in occupational medicine and neurology, or were dealt with by the Committee for Occupational Diseases. On the 27th January, 1977, The National Board of Industrial Injuries held a meeting, where the theme was, how to deal with "painter cases": Can brain atrophy be caused by solvents and is the disease found more frequently amongst painters? The meeting, which was assembled ad hoc, was held distinctly for the purpose of discussing this question. The participants were, apart from the management of The National Board of Industrial Injuries, medical consultants with a background in neurology and occupational medicine. These physicians proposed conducting a study involving 50 painters and a control group of 50 bricklayers, using the same design as a Swedish investigation conducted by the Department of Occupational Medicine in Ørebro, which had just been published (77). No decision was made regarding this suggestion, and the meeting then proceeded to deal with 15 notified cases, all of whom were painters with varying symptoms of poisoning.

Table 11. The number of notified and compensated cases of solvent-intoxication in Denmark 1976-94.

Year	Notified cases The work Injury register Danish Working Environment Service	Compensated cases The National Board of Industrial Injuries	Compensated cases %
1976	-	14	-
1977	-	22	-
1978	-	189	-
1979	-	308	-
1980	-	347	-
1981	-	414	-
1982	-	469	-
1983	-	501	-
1984	906	442	48.8
1985	1159	465	40.1
1986	1617	461	28.5
1987	1318	302	22.9
1988	1324	291	22.0
1989	1041	224	21.5
1990	773	154	19.9
1991	570	123	21.6
1992	530	119	22.5
1993	398	74*	-
1994	314	28*	-
Total	9950	4947	

*Incomplete figures because of non-finalized cases

One case, involving particularly massive exposure, had been acknowledged prior to the meeting, 2 were acknowledged during the meeting, and 3 were referred to further examination at the Department of Neurology at Rigshospitalet (The National Hospital of Denmark), where the examinations were to encompass CT-scanning, psychological testing and examination for neuropathy. The remaining cases were rejected. The conclusion of the meeting was that solvents can cause dementia ("as far as is known"), most often in the painting profession and others who work with organic solvents. It was decided that evaluation should take place on a case to case basis and that acknowledgement of the syndrome in each case should rest on 5 points in

particular:

1. Exposure duration
2. Working conditions at the place of employment
3. The Repeated occurrence of acute poisoning symptoms
4. The Absence of other illnesses
5. The Age of the injured person

These criteria were not specified more closely. The requirement that exposure duration should be at least 1 year was added at a later date.

In 1978, chronic solvent syndrome was added to the official list of occupational diseases, without any further specification of criteria. Thus, the criteria mentioned above, with the short exposure duration limit and imprecise criteria for medical and psychological diagnosing, were the only ones to be found. Classification as a listed disease means that the disease is recognised in each case for the purposes of compensation, unless it can be shown to be the result of something other than occupational conditions. This further means that it no longer becomes necessary to involve medical experts in each case, but that the treatment of such cases instead becomes, to a much greater extent, a purely administrative concern.

More precise criteria do not appear until 1989, when a set of guidelines, based on the results of Sigurd Mikkelsen's study, are formulated (125). It is established by these guidelines that there is no scientific evidence for an increased risk of brain damage, if exposure has involved less than 5-6 years of daily, full-time exposure to levels equalling current national limits, or, 18 years exposure to levels equalling 1/3 of these limits. The painting trade considers this lower exposure limit of 6 years to be the equivalent of 10 years of work as a construction painter, during the period when alkyd paints were primarily used. These guidelines further establish that when evaluating the degree of dementia, decisive weight should be placed on neuropsychological tests, and in particular, general reductions in performance on tests that are sensitive to brain damage. The adoption of this set of criteria in 1989 resulted in a clear tightening of administrative practice in cases concerning the recognition of solvent conditioned brain damage. Sigurd Mikkelsen's thesis was published in 1988. The results were known 1-2 years prior to publication, and, from this point in time, led gradually to more restrictive procedures.

The exact reasons as to why The National Board of Industrial Injuries acknowledged the

existence of solvent syndrome are not known officially. The epidemiological evidence that was available when it happened in 1977-78, i.e. scientific material concerning causal relations that normally form the basis for official recognition of occupational diseases, was without doubt insufficient at this time.

Table 11 also shows the number of cases of solvent poisoning notified to The Working Environment Service. Both cases of acute and chronic poisoning have to be reported to The Working Environment Service, while verified and suspected cases of chronic solvent syndrome have to be reported to The National Board of Industrial Injuries. During the whole of this period, doctors have been required to report occupational diseases to both The Working Environment Service and The National Board of Industrial Injuries, but they have done so to a lesser extent directly to The National Board of Industrial Injuries. In all essentials though, the number of compensation claims to The National Board of Industrial Injuries will be a proportion of the total number of cases reported to The Working Environment Service. In the extreme right-hand column of table 11 one can see the percentage of approved cases per year. These figures are based on the numbers in the first two columns, not on the individual cases' settlement, which often takes 1-2 years before a final decision is reached. It can be seen in table 11 that the percentage of cases recognised as brain damage has fallen during the period. The Working Environment Service's register does not provide us with official statistics before 1984. Before then there were very few work related injuries per year; through the 1970's and the first half of the 1980's there were 4-500 cases per year, consisting of all occupational diseases. When one considers table 1, one has to remember that the diseases in question have usually been preceded by 10-30 years of exposure. The large number of reported cases in the middle of the period contains, in part, a backlog of workers for whom there previously existed no apparatus of investigation.

10.4. The public and scientific debates.

In 1971 and 1972 two small books, the so-called painter reports, were published (3, 71). The first of these contains interviews with 20 construction painters. The second is a questionnaire study of 384 painters. Symptoms such as headache, dizziness, unnatural tiredness and memory difficulties were described, significantly more often by the most heavily exposed. These two reports were the result of an unusual cooperative venture between trade unions and students from the universities of Aarhus and Copenhagen. The two reports marked the start of a period stretching up through the 1970's and 80's in which a great deal of attention was directed towards

the working environment, both within trade unions and society in general. National unions and their local departments established work environment committees and employed people to deal with cases of occupational injury and the work environment. Painters' syndrome was the object of a large public debate, both within trade journals, the written daily press and broadcasting media. Painters' syndrome has been called the most talked about disease of the 80's in Denmark. In the mid-1980's one heard mention of thousands of workers with solvent syndrome; at this stage between 1,000 and 1,500 new cases were reported per year, while 4-500 per year received recognition entitling them to compensation. That the debate should become so widespread and intense is presumably due to several conditions of the time. There were a large number of exposed workers with diverse acute and sub-chronic toxic symptoms, who were therefore frequent visitors to general practitioners and trade unions. These persons represented a large proportion of the membership of unions for skilled workers, e.g. the Painters' Union, the Carpenters' and Joiners' Union and the unions for workers in the printing industry. The unions for unskilled workers, SiD and KAD, were also very aware of the problem. Furthermore, brain damage syndrome is a very dramatic disease, involving personality changes. Reduced intellectual functioning to the level of a moderate dementia means, in the case of a painter or metal worker, that the person is no longer able to undertake an ordinary job, and that his ability to function in many key areas of family and social life is severely diminished. The new alliance between trade unions and a section of the academic world, physicians, psychologists and engineers, has presumably also contributed to the intensity of the debate.

From the mid 1980's, a counter debate arose, which has occasionally flared up since. From the outset, the scientific evidence relating to chronic solvent syndrome was questioned. This discussion, however, quickly changed to a related but more questionable theme: "the over-diagnosing of painters' syndrome in Denmark". The debate was commenced with a paper aiming at a critical review of the Danish literature on organic solvents and presenile dementia. The authors, E.O. Errobo-Knudsen and F. Olsen, were both doctors with experience in occupational medicine and hygiene; the report was commissioned by The Danish Association of Oil Companies. The report reviewed 11 selected Danish publications on solvents from the period 1972-83 (57). Its conclusion was a rejection of the evidence for painter's syndrome, which, it was claimed, had been diagnosed as a result of a lack of regard for premorbid intellectual functioning in the psychological tests and an insufficient control for alcohol consumption. These issues were certainly relevant for a closer scientific evaluation and discussion. This was not the consequence

of the report, however. Instead, the two authors argued, on a dubious empirical foundation, that those persons who had started in the painting and decorating trade in the early 1960's were less intelligent than the average for their generation, and that painters and decorators had a greater alcohol consumption than others. The literature review was, overall, characterized by superficiality and deficiencies. At first it only achieved a very modest public impact, while the scientific press largely oversaw it. In 1986, however, the review was accepted for publication in the journal 'The Science of Total Environment', and has since then frequently been cited in the international literature with reference to the extremely high incidence of painters' syndrome in Denmark (57).

At the same time, a group of psychologists from Rigshospitalet (A. Gade et al) began to question the basis for diagnosing chronic painters' syndrome with psychological tests (66). An attempt was made to establish a set of neuropsychological test material from normal subjects for the purpose of creating reference data. When 20 persons who had previously been diagnosed with painters' syndrome were subsequently retested, it was found that the greater part of the established functional deterioration could not be confirmed when age, education and earlier intelligence were taken into account. In other words, when adjustments for these variables were made on the basis of the control material, the effect of exposure to solvents vanished, and one concluded therefore, that the cases in question should be viewed as false-positives.

This material started a long and often ardent debate about the diagnosis of dementia and general over-diagnosing of painters' syndrome in Denmark (45, 57). The main argument of Errebo-Knudsen et al (and several other physicians who joined the debate in the coming years) was "that medical diagnostics must have a natural science foundation, based on the results of objective tests that are compared with adequate reference material, allowing the separation of healthy and diseased functioning, and further, that this fundamental scientific principle of diagnosis has not been, and to a large extent is still not, applied in the psychological diagnosing of dementia, which, on the contrary, is arbitrary, unscientific, subjective, opinion based, clinical diagnosing, that has led to the over-diagnosing of dementia" (45).

The counter argument from a large circle of Danish psychologists has been, that the diagnosing of brain damage requires more than the simple comparison of test results from a patient with relevant reference material; that the problem is, on the contrary, more complex, and requires a

composite evaluation of cognitive functioning and personality (2). Diagnosis should rest upon the patient's case history, previous and present functioning, neuropsychological testing and a clinical evaluation of mental state and behaviour in the test situation, combined in both a qualitative and quantitative evaluation.

The debate has continued since 1984 in both the medical and psychological journals. Its most recent manifestation came in 1994, when Errebo-Knudsen et al's complaint to the Committee of Scientific Dishonesty and Good Scientific Practice was rejected, on the grounds that the discussion has solely concerned the usefulness of an applied scientific method that, in addition, has been openly displayed for the purpose of professional discussion (37).

It is unlikely that this 10-year long debate has altered many opinions and it has not aided clarification of the issues to any worthwhile extent, let alone contributed to finding solutions for the unresolved questions that still exist in the diagnosing of brain damage. It started with a deficient review, solely of the Danish literature, that raised the question of the existence of chronic solvent syndrome. This theme has occasionally been reintroduced for debate. It can be said, however, that there now exists general agreement between Danish physicians and psychologists and in the relevant scientific societies, that the evidence regarding the existence of chronic solvent syndrome is sufficiently convincing. There is also reasonably widespread agreement as to the need for better techniques for diagnosing dementia, for a standardised test battery and adequate reference material. Even so, these still do not exist in Denmark today. Gade's material from the early 1980's is too small and can be criticised on other grounds too. It consisted of test results from 120 hospital patients, some of whom had recently undergone operations requiring anaesthetics (66). This situation can be compared with Sweden, where one has used a standardised test battery since the late 1970's and also possessed a larger set of normal reference material. Even so, a gradual narrowing of the criteria for diagnosing dementia for compensation purposes has undoubtedly occurred in Denmark, most recently with The National Board of Industrial Injuries' new guidelines from 1989, so that we hardly differ in any substantial way from Sweden today. It is equally certain that the diagnosis of brain damage, and its recognition by The National Board of Industrial Injuries over the past 10 years, has relied on looser diagnostic criteria and a lower diagnostic threshold.

11.0. The relationship between the solvent syndrome debate and the regulatory authorities.

The discussion about solvents and brain damage was hastened by the appearance of the two student reports from 1971 and 1972, and later, by the medical studies of the mid-1970's. The debate was, from the very start, conducted just as much via the daily press as in professional and scientific papers. It quickly acquired the nature of a general debate about occupational injuries and the work environment. The present structure of the Danish occupational health services was built up from 1977 and thereafter. Previously there had only existed a single department of occupational medicine, which had been established at Rigshospitalet in 1946. From 1977-1987, departments of occupational medicine were established in every county in the country. The Occupational Health Services were also established in the same period, starting in 1978. This kind of system for examining patients, conducting research and undertaking preventive measures had already been in existence for some years in countries like Sweden and Finland. It seems probable that the timing of the establishment of an occupational health system in Denmark is related to the intense debate about occupational injuries in general and solvents in particular. The recognition of the many solvent injuries also entailed economic consequences. From 1978-89, 2.1 billion Dkr were payed out in compensation to persons with brain damage following exposure to solvents. This sum represents half the entire amount paid in compensation to people with occupational diseases in this period. The survival of one branch in particular was threatened, namely the painting and decorating trade, not because of compensation claims, which is an insurance matter, but because of a shortage of labour, resulting from the many diagnosed cases of brain damage and subsequent removal from the workforce of painters and decorators receiving invalidity pensions.

An early initiative aiming at the regulation of solvents was taken by the authorities in the form of bulletins and announcements, and by making it a priority area for the Working Environment Service. As far back as in 1967, a committee was instituted in the Working Environment Service, on the basis of complaints from trade unions and with representatives from the painting and decorating branch's employers' and employees' organisations, as well as from the paint industry. The first declaration concerning the handling of paints came in 1968 and contained directions for the use of personal protective equipment, which were not, however, particularly restrictive. For example, the use of filter masks was not recommended unless more than 5 litres of alkyd paint

was used indoors per day. Considerably more exacting rules concerning protective equipment and product substitution have subsequently appeared, as has the system of labelling paint products, the so-called MAL-code. Rules about substitution were introduced in the Ministry of Labour's declaration on chemicals and substances in 1982. Here, the toxicity of chemical substances is stipulated, on the basis of scientific data from animal experiments and epidemiological studies. Emphasis is put on long-term effects rather than acute toxicity, upon which one had previously focussed. In the rule about substitution it is stated:

1. "A chemical or substance that may be a hazard to health or otherwise diminish safety must not be used, if it can be substituted by a hazardless, less hazardous or less troublesome chemical or substance.
2. When the use of a substitute chemical or substance entails considerable differences in technical properties or expenses, a composite evaluation of the technical or economic consequences versus the safety and health related concerns must be made".

The intervention by the authorities and the debate about solvents, which was also taking place in no small way at company level, led to demands on manufacturers and distributers for substitute chemicals and methods. Work on the development of new products was started in some areas, while other areas saw the reintroduction of old methods. An intense period of product development by the Danish paint and lacquer factories resulted in products, such as water-based acrylic paints, that are in use today. The outcome was a quite rapid shift in consumption patterns. The consumption of solvent-based paints within the painting and decorating trade peaked in 1970 at 18,000 tons per year; 12 years later in 1982, this figure was down to 2 tons per year. The consumption of water-based paints has undergone a comparable, but inverted, course of development. Today, 90% of all paint used in the building and decorating trade is water-based. A radical substitution of products and methods has also occurred with the degreasing and cleaning of metals, where the shift has been towards high-pressure hosing with water and washing with alkaline soap solutions, or, in the case of the typographical industry, the use of soya oil for cleaning rollers. The last 20 years has also witnessed a significant substitution of the worst solvents with less dangerous types, such as alcohols and glycols, which evaporate less readily (78, 116).

In some classical areas of chlorinated solvent usage a "back and forth substitution" process has occurred in the last 20 years. In dry-cleaning, a health related substitution from perchloroethylene to freon took place, while TRI was substituted with 1,1,1-trichloroethane and freon for metal

cleaning. As a consequence of the fact that freon, and subsequently 1,1,1-trichloroethane, were discovered to be ozone degenerating, they were fazed out of the work environment in Denmark and most other industrialised countries. A ban against the use of freon was introduced in Denmark on the 1st January, 1995, while 1,1,1-trichloroethane was banned on the 1st January 1996. One has now returned to using the old chlorinated solvents; a move made out of concern for the external environment, but a backwards step for work health and safety. In quantitative terms however, this is a minor case, which does not alter the general trend towards the regulation of chlorinated solvent use in the work place.

It is The National Agency of Environmental Protection that coordinates the use of organic solvents with regard to their influence on the environment. Initiatives have been taken in two areas. First, one has attempted to inform and regulate consumption through labelling; The National Agency of Environmental Protection has especially attempted to influence the labelling policies of the European Union, thus far without success, with the R48 clause on risk: "Danger of serious risk to health by prolonged exposure" (78). Secondly, one has limited the emission to the outer environment of the most dangerous organic solvents. An agreement has been reached with industry on a 40% reduction in the release of organic solvents by 1999. The latest initiative is the introduction of "green taxes". From the 1st January 1996 a special tax is to be paid on the use of TRI, perchloroethylene and methylene chloride, the level being 2 Dkr per kg of imported chlorinated solvent.

The Working Environment Service has made persistent efforts in this area with the development of rules and regulations, a campaign focussing on the issue in 1985, workplace inspections and injunctions. This has been followed up by the Occupational Health Services' practical advice about substitution and ventilation. To reduce exposure even further, the threshold limit values have been reduced significantly in recent years. In Sweden these limits have been halved for all solvents that have been scientifically documented to have long-term health effects, primarily brain damage. In Denmark limits for organic solvents were reduced on the 1st July 1994 by between 25 and 75%, according to the toxicity of the individual substance.

Organic solvents are still extensively used in occupational settings in Denmark, but in the vast majority of cases they have been regulated to a level that does not entail risk for the development of chronic solvent syndrome. The changes have occurred over a relatively short time span of 15-

20 years. In no other area has the Danish work environment been regulated with so short a delay following, or almost before, the establishment of scientific evidence concerning a health hazard. A complex interplay of events and conditions underlies these developments. An important element has been the increased level of awareness concerning work environment issues, and, later on, environmental issues in a broader sense, that has arisen in the Danish work place and spread to society in general since the late 1970's. Attitudes on the environment have, to a high degree, developed on the foundation laid by the discussion about organic solvents. Popular demand for a safe working environment, free of the risk of brain damage, was quickly transformed into political demands, whose importance for the early efforts of the Working Environment Service, and The National Board of Industrial Injuries' rapid acceptance of the brain damage diagnosis, should not be underestimated. In any case, the result has been a considerable preventive effort aimed at solvents in the Danish work environment. It is also one of the few examples of how the occupational injury system is able to contribute to prevention. The story is in several ways a mile stone in the recent history of Danish occupational medicine.

12.0. References.

I Rasmussen K, Sabroe S. Neuropsychological symptoms among metal workers exposed to halogenated hydrocarbons. Scand J Soc Med 1986;14:161-8.

II Rasmussen K, Jeppesen HJ, Sabroe S. Solvent-induced chronic toxic encephalopathy. Am J Ind Med 1993;23:779-92.

III Rasmussen K, Jeppesen HJ, Sabroe S. Psychometric tests in assessment of brain function after solvent exposure. Am J Ind Med. 1993; 24:553-565.

IV Rasmussen K, Sabroe S, Arlien-Søborg P. Clinical neurological findings among metal degreasers exposed to chlorinated solvents. Acta Neurol Scand 1993;87:200-4.

V Rasmussen K, Brogren CH, Sabroe S. Subclinical affection of liver and kidney function by solvent exposure. Int Arch Occup Environ Health 1993;64:445-8.

VI Rasmussen K, Sabroe S, Wohlert M, Ingerslev HJ, Kappel B, Nielsen J. A genotoxic study of metal workers exposed to thrichloroethylene. Sperm parameters and chromosome aberrations in lymphocytes. Int Arch Occup Environ Health 1988;60:419-23.

VII Christensen JM, Rasmussen K. Danske arbejderes udsættelse for triklorethylen 1947-87. Ugeskr Læger 1990;152:464-7.

1. Andersen R. Verbal and visuo-spatial memory. Scand J Psychol 1976;17:198-204.

2. Andersen R et al. Occupational toxic encephalopati. (In Danish). Ugeskr Laeger 1987; 149:1471.

3. Andersen S et al. Painters report Copenhagen 1972. (In Danish). Copenhagen: The painters union, 1972.

4. Andersson A. Health dangers in industry by exposure to trichoroethylene. (In German). Acta Med Scand 1957;157 (suppl. 323):1-165.

5. Anger WK. Neurobehavioral tests used in NIOSH-supported worksite studies 1973-1983. Neuro Toxicol Teratol 1985;7:359-68.

6. Annau Z. The neurobehavioral toxicity of trichloroethylene. Neurobehav Toxicol Teratol 1981;3:417-24.

7. Arlien-Søborg P, Zilstorff K, Grandjean B, Pedersen LM. Vestibular dysfunction in occupational chronic solvent intoxication. Clin Otolaryngol 1981;6:285-90.

8. Arlien-Søborg P. Trichloroethylene. In: Solvent Neurotoxicity. Florida: CRC Press, 1992.

9. Arlien-Søborg P, Bruhn P, Melgård B. The chronic painters syndrome. Toxic dementia among painters. (In Danish). Ugeskr Laeger 1978: 140:1645-49.

10. Arlien-Søborg P. Organic solvents and the nervous system. Report on a conference sponsored by the Commission of the European Communities and the Danish Ministry of Environment. Luxembourg: The Commission of the European Communities. Directorate-General for Employment, Social Affairs and Education, 1991.

11. Armitage P. Test for linear trends in proportions and frequencies. Biometrics 1955;11:375-86.

12. Axelson O, Hane M, Hogstedt C. A case referent study on neuropsychiatric disorders among workers exposed to solvents. Scand J Work Environ Health 1976;2:14-20.

13. Axelson O, Andersson K, Hogstedt C, Holmberg B, Molina G, Deverdier A. A cohort study on trichloroethylene exposure cancer mortality. J Occup Med 1978;20:194-6.

14. Axelson O, Selden A, Anderssen K, Hogstedt C. Updated and expended swedish cohort study of trichloroethylene and cancer risk. J Occup Med 1994; 36:556-62.

15. Baker EL, White RF, Murawski BJ. Clinical evaluation of neurobehavioral effects of occupational exposure to organic solvents and lead. Int J Ment Health 1985;14:135-58.

16. Baker EL, Letz R. Neurobehavioral testing in monitoring hazardous workplace exposures. J Occup Med 1986;28:987-90.

17. Baker EL, Feldman RG, White RF, Harley JP, Dinse GE, Berkey CS. Monitoring neurotoxins in industry: Development of a neurobehavioral test battery. J Occup Med 1983;25:125-130.

18. Baker EL, Seppäläïnen M. Human aspects of solvent neurobehavioral effects. Neurotoxicology 1987;7:43-56.

19. Bardodej Z, Vyskocil J. The problem of trichloroethylene in occupational medicine. AMA Arch Ind Health 1956;13:581-92.

20. Barret L, Garrel S, Danel V, Debru JL. Chronic trichloroethylene intoxication: A new approach by trigeminal-evoked potentials? Arch Environ Health 1987;42:297-302.

21. Barret L, Faure J, Guillard B, Chornat D, Didier B, Debou J. Trichloroethylene occupational exposure: elements for better prevention. Int Arch Occup Environ Health 1984;53:283-289.

22. Bernard AM, Roels H, Cardenas A, Lauwerys R. Assessment of urinary protein 1 and transferin as early markers of cadmium nephrotoxicity. Br J Ind Med 1990;47:559-65.

23. Bjerrehus T, Detlefsen GV. Infertility in Danish painters exposed to organic solvents. (In Danish). Ugeskr Læger 1986;148:1105-6.

24. Bleecker ML, Bolla KI, Agneu J, Schwartz BS, Ford PD. Dose-related subclinical neurobehavioral effects of chronic exposure to low levels of organic solvents. Am J Ind Med 1991;19:715-28.

25. Bloom S, Till S, Sønksen P, Smith S. Use of biothesiometer to measure individual vibration thresholds and their variation in 519 non-diabetic subjects. Br Med J 1984;288:1793-5.

26. Bolla KI, Schwartz BS, Agneu J, Ford PD, Bleecker ML. Subclinical neuropsychiatric effects of chronic low-level solvent exposure in US paint manufacturers. J Occup Med 1990;32:671-7.

27. Bonnevie P. From the working field of the department of occupational medicine. Solvent intoxication (in Danish). Ugeskr. Laeger 1952; 114,61.

28. Bonnevie P. Hygiene (in Danish). Copenhagen: Nyt Nordisk Forlag, 1951.

29. Brackbill RM, Maizlish N, Fishbach T. Risk of neuropsychiatric disability among painters in the United States. Scand J Work Environ Health 1990;16:182-8.

30. Brandt L, Kolstad H, Rasmussen K. Health risks by dry cleaning. (In Danish). Ugeskr. Laeger 1987; 149:319-23.

31. Breslow NE, Day NE. Statistical Methods in Cancer Research. Lyon: IARC Scientific Publications no. 32, 1980.

32. Brinkworth MH, Wardley-Jones A, Edwards AJ, Hughes JA, Andersson D. A comparison of smokers and non-smokers with respect to oncogene products and cytogenetic parameters. J Occup Med 1992;34:1181-7.

33. Brogren C-H, Christensen JM, Rasmussen K. Occupational exposure to chlorinated organic solvents and its effect on the renal excretion of N-Acetyl-Beta-D-Glucosaminidase. Arch Toxicol 1986;suppl. 9:460-64.

34. Bruckner JV, Davis BD, Blancato JN. Metabolism, toxicity and carcinogenecity of trichloroethylene. Toxicology 1989;20:31-50.

35. Bruhn P, Gade S. Extended manual of neuropsychological testing. (In Danish). Copenhagen: National Hospital, 1980.

36. Buxton PH, Hayward M. Polyneuritis cranialis associated with industrial trichloroethylene poisoning. J Neurol Neurosurg Psychiatr 1987;30:511-8.

37. Brydensholt HH. Toxic encephalopathi and scientific dishonoursty (in Danish). Ugeskr Laeger 1994; 156:352.

38. Cambell DD, Lockey JE, Pebajan J, Gunter BJ, Rom WN. Health effects among refrigeration repair workers exposed to fluorocarbons. Br J Ind Med 1986;43:107-11.

39. Carrano AV. Chromosomal alterations as markers of exposure and effect. J Occup Med 1986;28:1112-6.

40. Cavanagh JB, Buxton PH. Trichloroethylene cranial neuropathy: is it really a toxic neuropathy or does it activate latent herpes virus? J Neurol Neurosurg Psychiatr 1989;52:297-303.

41. Chen JD, Wang JD, Jang JP, Chen YY. Exposure to mixtures of solvents among paint workers and biochemical alterations of liver function. Br J Ind Med 1991;48:696-701.

42. Cherry N, Waldron HA. The prevalence of psychiatric morbidity in solvent workers in Britain. Int J Epidem 1984;13:197-200.

43. Christensen AL. Luria's Neuropsychological Investigation. Copenhagen: Munksgaard, 1974.

44. Christensen JM, Rasmussen K, Köppen B. Automatic headspace gas chromatographic method for the simultaneous determination of trichloroethylene and metabolites in blood and serum. J Chromatogr 1988;442:217-23.

45. Clemmensen J, Errebo-Knudsen EO, Holma B, Hyllested K, Olsen F, Snorrason E. The painters syndrome or presenile dementia - an enormous overdiagnostication with great human and economical costs (in Danish). Ugeskr Laeger 1991: 153:123-25.

46. David NJ, Wolman R, Milne FJ, Niekerk IV. Acute renal failure due to trichloroethylene poisoning. Br J Ind Med 1989;46:347-9.

47. Daniell W, Stebbins A, O'Donnell J, Horstman SW, Rosenstock L. Neuropsychological performance and solvent exposure among car body repair shop workers. Br J Ind Med 1993;50:368-77.

48. Dekant W, Metzler M, Henschler D. Novel metabolites of trichloroethylene through dechlorination reaction in rats, mice and armans. Biol Pharmacol 1984;33:2021-7.

49. Demers RY, Markell BL, Wakebe R. Peripheral vibratory sense deficits in solvent exposed painters. J Occup Med 1991;33:1051-4.

50. Driscoll TR, Hamdan HH, Wang G, Wright PFA, Stacey NH. Concentrations of individual serum or plasma bile acids in workers exposed to chlorinated aliphatic hydrocarbons. Br J Ind Med 1992;49:700-5.

51. Døssing M, Arlien-Søborg P, Petersen LM, Ranek L. Liver damage associated with occupational exposure to organic solvents in house painters. Eur J Clin Invest 1983;13:151-7.

52. Edling C, Annundi H, Johansson G, Nielsson K. Increase in neuropsychiatric symptoms after occupational exposure to low levels of styrene. Br J Ind Med 1993;50:843-50.

53. Ellermann M, Jacobsen J.A clinical investigation of symptoms of intoxications by DUCO Lackering. (In Danish). Hospitalstidende 1933: 76:1213-21.

54. Elofsson S-A, Gambrale F, Hindmarsh T et al. Exposure to organic solvents: A cross-sectional epidemiologic investigation on occupationally exposed car and industrial spray painters with special reference to the nervous system. Scand J Work Environ Health 1980;6:239-73.

55. El Ghawabi, Mansor MB, El Gamel MS, El Saharti AA, EE Enany FF. Chronic trichloroethylene exposure. J Egypt Med Assoc 1973;56:715-24.

56. Environmental Protection Agency. Health Assessment Document for Trichloroethylene. EPA/600/8-82/006F, Final Report, Research Triangle Park, NC, USA 1985.

57. Erreboe-Knudsen EO, Olsen F. Organic solvents and presenile dementia (The Painters syndrome). A critical review of the Danish litterature. Science tot. Environ 1986; 48:45-67.

58. Errebo-Knudsen EO, Olsen F. The organic solvent syndrome. How many false positive diagnosis? (in Danish). Ugeskr Laeger 1982; 148:284-85.

59. Feldman RG, White RF, Currie JN, Travers PH, Lessell S. Long-term follow-up after single toxic exposure to trichloroethylene. Am J Ind Med 1985;8:119-26.

60. Feldman RG, Mayer RM, Taub A. Evidence for peripheral neurotoxic effect of trichloroethylene. Neurology 1970;20:599-606.

61. Fidler A, Baker EL, Letz RE. Neurobehavioral effects of occupational exposure to organic solvents among construction painters. Br J Ind Med 1987;44:292-308.

62. Franchini I, Cavatorta A, Falzoni M, Lucertini S, Mutti A. Early indicators of renal damage in workers exposed to organic solvents. Int Arch Occup Environ Health 1983;52:1-9.

63. Franco G, Fonte R, Tempini G, Canduar F. Serum bile acid concentrations as a liver function test in workers occupationally exposed to organic solvents. Int Arch Occup Environ Health 1986;58:157-64.

64. Franco G. New perspectives in biomonitoring liver function by means of serum bile acids: experimental and hypothetical biochemical basis. Br J Ind Med 1991;48:557-61.

65. Frederiksson M, Bentsson NO, Hardell L, Axelsson O. Colon cancer, physical activity and occupational exposures. A case-control study. Cancer 1989;63:1838-42.

66. Gade A, Mortensen EL, Bruhn P. Chronic painters syndrome. A reanalysis of psychological test data in a group of diagnosed cases, based on comparisons with matched controls. Acta Neurol Scand 1988;77:293-306.

67. Gamberale F. Use of behavioral performance tests in the assessment of solvent toxicity. Scand J Work Environ Health 1985;11, suppl. 1:65-74.

68. Gamberale F, Annwall G, Anshelm Olson B. Exposure to trichloroethylene III. Psychological functions. Scand J Work Environ Health 1976;4:220-4.

69. Glass RI, Lyness RN, Mengle DC, Powell KE, Kahn Z. Sperm count depression in pesticide applicators exposed to dibromochloropropane. Am J Epid 1979;109:346-51.

70. Gloerfelt-Tarp K, Bonnevie P, Wagner L. Workers Protection (in Danish). Copenhagen: Martins Forlag, 1943.

71. Glud T, Jensen P, Nielsen N. The painters report. (In Danish). Aarhus: The Students Council University of Aarhus, 1971.

72. Grandjean E, Münchinger R, Rurrian V, Haas PA, Knoepfel H-K, Rosenmund H. Investigations into the effects of exposure to trichloroethylene in mechanical engineering. Br J Ind Med 1955;12:131-42.

73. Gregersen P, Mikkelsen S, Klausen H. Døssing M, Nielsen H, Thygesen P. A chronic cerebral syndrome in painters. Dementia due to inhalation or of cryptogenic origin? (In Danish). Ugeskr Laeger 1978; 140:1638-44.

74. Gu ZW, Sele B, Chmara D et al. Effects of trichloroethylene and its metabolites on the rate of sister-chromatic exchange. In vivo and in vitro study on the human lymphocytes. (In French) Ann Génét 1981;24:105-6.

75. Gubéran E, Usel M, Raymond L, Tissot R, Sweetnam PM. Disability, mortality, and incidence of cancer among Geneva painters and electricians: a historical prospective study. Br J Ind Med 1989;46:16-23.

76. Guzelian P, Mills S, Fallon H. Liver structure and function in print workers exposed to toluene. J Occup Med 1988;30:791-6.

77. Hane M, Axelsson O, Blume J, Hogstedt C, Sundell L, Ydreborg B. Psychological function changes among house painters. Scand J Work Environ Health 1977;3:91-9.

78. Hansen TB, Gregersen P. Organic solvents. Environmental project no. 70. Copenhagen: The National Agency of Environmental Protection, 1986.

79. Hardell L, Eriksson M, Lenner P, Lundgren E. Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: a case-control study. Br J Cancer 1981;43:169-76.

80. Halevy J, Pitlik S, Rosenfeld J. 1,1,1-trichloroethane intoxication: A case report with transient liver and renal damage. Review of the literature. Clin Toxicology 1980;16:467-92.

81. Hartman DE. Neuro-psychological Toxicology. Identification and Assessment of Human Neurotoxic Syndromes. New York: Pergamon Press, 1988.

82. Heath CW, Dumont CR, Gamble J, Waxweiler R. Chromosomal damage in men occupationally exposed to vinyl chloride monomer and other chemicals. Environ Res 1977;14:68-72.

83. Hogstedt C, Axelsson O. Long-term health effects of industrial solvents - a critical review of the epidemiological research. Med Lav 1986;77:11-22.

84. Hogstedt C, Anderson K, Haru M. A questionnaire approach to the monitoring of early disturbances in central nervous functions. In: Aito A, Riikimäki V, Vainio H (eds.). Biological monitoring and surveillance of workers exposed to chemicals. Washington: Hemisphere Publishing Corporation 1984;275-87.

85. Hogsted C. Has the Scandinavian solvent syndrome controversy been solved? Scand J Work Environ Health 1994: 20:59-64.

86. Husman K, Karli R. Clinical neurological findings among carpainters exposed to a mixture of organic solvents. Scand J Work Environ Health 1980;6:33-9.

87. Hänninen H, Eskelinen L, Husman K, Nurminen M. Behavioral effects of long-term exposure to a mixture of organic solvents. Scand J Work Environ Health 1976;2:240-55.

88. Hänninen H. Psychological picture of manifest and latent carbon disulfide poisoning. Br J Ind Med 1971;28:374-81.

89. Hänninen H, Lindström K. Behavioral test battery for toxicopsychological studies". Helsinki: Institute of Occupational Health, 1979.

90. Kapp RW, Jacobsen CB. Analysis of human spermatozoa for Y-chromosomal non-disjunction. Teratog Carcinog Mutag 1980;1:193-211.

91. Kirch W, Shwarz W, Gizycki CV. Congestive cardiomyopathy due to chronic inhalation of trichloroethylene. Arch Toxicol 1982;suppl. 5:322-5.

92. Konietzko H, Haberlandt W, Reill G, Weichardt H. Chromosome studies and trichloroethylene workers. (In German). Arch Toxicol 1978;40:201-6.

93. Konietzko H, Elster I, Sayer H, Weichardt H. Damages to the central nervous system through trichloroethylene. (In German). Staub-Reinhalt Luft 1975;35:240-1.

94. Kurpa K, Husman K. Car painters' exposure to a mixture of organic solvents. Scand J Work Environ Health 1982;8:137-40.

95. Lajer M. Investigation of symptoms in house painters at their work sites. (In Danish). Ugeskr Laeger 1976; 138: 1225-30.

96. Lancranjan I, Popescu HI, Gavanescu O, Klepsch I, Serbanescu M. Reproductive ability of workmen occupationally exposed to lead. Arch Environ Health 1975;30:396.

97. Lash A, Becker CE, Su V, Shore M. Neurotoxic effects of mehylene chloride: Are they long lasting in humans? Br J Ind Med 1991;48:418-26.

98. Lauwerys RR, Bernard A. Early detection of nephrotoxic effects of industrial chemicals. State of the art and future prospects. Am J Ind Med 1987;11:275-85.

99. Lawrence WH, Partyka EK. Chronic dyshagia and trigeminal anaesthesia after trichloroethylene exposure. An Int Med 1981;95:710.

100. Lezak MD. Neuropsychological Assessment. New York: Oxford University Press, 1983.

101. Lezak MD. Neuropsychological assessment in behavioral toxicology - developing techniques and interpretation issues. Scand J Work Environ Health 1984;10, suppl.: 1:25-29.

102. Lilis R, Stanescu D, Muica N, Roventa A. Chronic effects of trichloroethylene exposure. Med Lavoro 1969;60:595-601.

103. Lindh T, Nevarsson U, Vesterberg O. Trends over several decades in excretion of trichloroacetic acid after occupational exposure to trichloroethylene. Congress Report on Solvents. National Institute of Occupational Health. Stockholm 1986.

104. Lindström K. Psychological performance of workers exposed to varius solvents. Work Environ Health 1973: 10:151-155.

105. Lindström K, Riihimäki H, Hänninen H. Occupational solvent exposure and neuropsychiatric disorders. Scand J Work Environ Health 1984;10:321-3.

106. Lishman WA. Organic Psychiatry. The psychological consequences of cerebral disorder. Blackwell Scientific Publications. Oxford 1978.

107. Liu YT et al. Increased subjective symptoms prevalence among workers exposed to trichloroethylene at sub-OEL levels. Tokoku J Exp Med 1988;155:183-95.

108. Lun A, Schmidt P. Liver damage caused by 1,1,2-trifluoro-1,2,2-trichloroethane. (In German). Dtsch Gesundhedsheitswes. 1979;34:1679-82.

109. Lundberg I, Gustavsson A, Högberg M, Nise G. Diagnosis of alcohol abuse and other neuropsychiatric disorders among house painters compared with house carpenters. Br J Ind Med 1992;49:409-15.

110. Lundbjerg I, Håkansson M. Normal serum activities of liver enzymes in Swedish print industry workers with heavy exposure to organic solvents. Br J Ind Med 1985;42:596-600.

111. Lundberg I et al. Neuropsychiatric function of house painters with previous long-term heavy exposure to organic solvents. Scand J Work Environ Health 1995; suppl 1: 44 p.

112 Lundström R, Strömberg T, Lundborg G. Vibrotactile perception threshold measurements for diagnosis of sensory neuropathy. Description of a reference population. Int Arch Occup Environ Health 1992;64:201-7.

113. Maizlish NA, Langolf GD, Whitehead LW et al. Behavioral evaluation of workers exposed to mixtures of organic solvents. Br J Ind Med 1985;42:579-90.

114. Mccunney RJ. Diverse manifestations of trichloroethylene. Br J Ind Med 1988;45:122-6.

115. Meyer BR, Fishbein A, Rosenman K, Lerman Y, Drager DE, Reidenberg MM. Increased urinary enzyme excretion in workers exposed to nephrotoxic chemicals. Am J Med 1984;76:989-98.

116. Mikkelsen AB, Petersen R, Rasmussen K, Sabroe S. Chlorinated solvents - a work environment problem. (In Danish). Copenhagen: Fremad, 1983.

117. Mikkelsen S, Jørgensen M, Browne E, Gyldensted C. Mixed solvent exposure and organic brain damage. A study of painters. Acta Neurol Scand 1988;78:suppl. 118;1-143.

118. Mikkelsen S. A cohort study of disability pension and death among painters with special regard to disabling presenile dementia as an occupational disease. Scand J Soc Med 1980;suppl. 16:34-43.

119. Mitchell ABS, Parssons-Smith BG. Trichloroethylene neuropathy. Br Med J 1969;1:422-3.

120. Müller G, Spassowski M, Henschler D. Metabolism of trichloroethylene in man II. Pharmacokinetics of metabolites. Arch Toxicol 1974;32:283-95.

121. Müller G, Spassowski M, Henschler D. Metabolism of trichloroethylene in man. III. Interaction of trichloroethylene and ethanol. Arch Toxicol 1975;33:173-89.

122. Nagaya T, Ishikawa N, Hata H. Urinary total protein and β-2-microglobulin in workers exposed to trichloroethylene. Envir Research 1989;50:86-92.

123. Nagaya T, Iskikawa N, Aata H, Otobe T. Subclinical and reversible hepatic effects of occupational exposure to trichloroethylene. Int Arch Occup Environ Health 1993;64:561-3.

124. Nagaya T, Ishikawa N, Hata H. Sister-chromatic exchanges in lymphocytes of workers exposed to trichloroethylene. Mutat Research 1989;222:279-82.

125. National Board of Industrial Injuries. Declaration for decissions in cases of brain damage after work with solvents. (In Danish). Copenhagen: National Board of Industrial Injuries 1989.

126. Ng TP, Lam WK, Jones GM. Neurobehavioral effects of industrial mixed solvent exposure in Chinese printing and paint workers. Neurotoxicol Teratol 1990;12:661-4.

127. Nielsen J, Wohlert M, Faaborg-Andersen J et al. Incidence of chromosome abnormalities on newborn children. Comparison between incidences in 1969-1974 and 1980-1982 in the same area. Hum Genet 1982;61:98-101.

128. Nikula E, Kiviniitty K, Leisti J, Taskinen PJ. Chromosome aberrations in lymphocytes of nurses handling cytostatic agents. Scand J Environ Health 1984;10:71-4.

129. O'Flynn RR, Monkman SM, Waldron HA. Orignis solvents and presenile dementia: a case referent study using death certificates. Br J Ind Med 1987;44:259-62.

130. O'Flynn RR, Waldrom HA. Delpech and the origin of occupational psychiatry. Br J Ind Med 1990, 47:189-98.

131. Olsen E, Seedorf L, Laursen B. Organic solvents, a survey of employment and the occurrence of vapours. (In Danish). Danish National Institute of Occupational Health, report no. 26, Copenhagen 1986.

132. Olsen J, Sabroe S. A case-reference study of neuropsychiatric disorders among workers exposed to solvents in the Danish wood and furniture industry. Scand J Soc Med 1980;suppl. 16:44-9.

133. Olson BA, Gamberale F, Grönqvist B. Reaction time changes among steel workers exposed to solvent vapors. Int Arch Occup Environ Health 1981;48:211-18.

134. Plessner W. About trigeminal disease from exposure to trichloroethylene. (In German). Neurol Zbl 1915;34:916.

135. Porro A, Lomonte C, Coratelli P, Passavanti G, Ferri GM, Assennato G. Chronic glomerulonephritis and exposure to solvents: a case-referent study. Br J Ind Med 1992;49:738-42.

136. Price RG. Urinary enzymes, nephrotoxicity and renal disease. Toxicology 1982;23:99-134.

137. Raffi GB, Violante FS. Is freon 113 neurotoxic? A case report. Int Arch Occup Environ Health 1981;49:125-7.

138. Rasmussen H, Olsen J, Lauritsen J. Risk of encephalopatia among retired solvent-exposed workers. J Occup Med 1985;27:561-6.

139. Rasmussen K, Bjerre A, Petersen R, Sabroe S. Health complaints caused by working with chlorinated solvents in the electronic industry (In Danish). Ugeskr Laeger 1985;47:1053-6.

140. Rasmussen K, Sabroe S. Health risks involved in metal degreasing with chlorinated solvents. A cross-sectional investigation. (In Danish). Ugeskr Laeger 1985;147:3721-7.

141. Rasmussen K, Jeppesen HJ, Arlien-Søborg P. Psychoorganic syndrome from exposure to fluorocarbon 113 - an occupational disease? Eur Neurol 1988;28:205-7.

142. Ravnskov V. Glomerulonephritis and organic solvents (in Swedish). Läkartidningen 1986;83:1080-3.

143. Riise T, Moen B. A nested case-control study of disability pension among seamen, with special reference to neuropsychiatric disorders and exposure to solvents. Neuroepidemiology 1990;9:88-94.

144. Ruijten MW, Verberk MM, Sallé HJA. Nerve function in workers with long-term exposure to trichlorothylene. Br J Ind Med 1991;48:87-92.

145. Sabroe S, Olsen J. Mental function changes among solvent exposed cabinet makers. (In Danish). Ugeskr Laeger 1979; 141:322-7.

146. Sagawa K, Nishitani H, Kawai H, Kuge Y, Ikeda M. Transverse lesion of spinal cord after accidental exposure to trichloroethylene. Int Arch Arbeitsmed 1973;31:257-64.

147. Salvini M, Binaski S, Riva M. Evaluation of psychophysiological function in humans exposed to trichloroethylene. Br J Ind Med 1971;28:293-5.

148. Schioetz EH. Intoxication by trichloroethylene ("TRI") with special reference to dry cleaning shops. (In Norwegian). Nord. Med. Tidskr 1938; 15:808-13.

149. Seiji K, Jin C, Watanabe T, Nakatsuka H, Ikeda M. Sister chromatic exchanges in peripheral lymphocytes of workers exposed to benzene, trichloroethylene or tetrachloroethylene with reference to smoking habits. Int Arch Occup Environ Health 1990;62:171-6.

150. Shibayama H, Kitoh J, Marni Y, Kobyaski H, Iwase S, Kayakawa V. An unusual case of Pick's disease. Acta Neuropathol 1983;59:79-87.

151. Skogstad M, Kristensen P. Trikloreten (In Norwegian). National Institute of Occupational Health, Stockholm 1991. Arbete & Hälsa 1991;43.

152. Smith GF. Investigation of the mental effects of trichloroethylene. Ergonomics 1970;13:580-6.

153. Solet D, Robin TG. Renal functions in dry-cleaning workers exposed to perchloroethylene. Am J Ind Med 1991;20:601-14.

154. Spencer PS, Schaumburg HH. Organic solvent neurotoxicity. Facts and research needs. Scand J Work Environ Health 1985;suppl. 1:53-60.

155. Spurgeon A, Gray CN, Sims J, Calvert I, Levy LS, Harvey PG, Harrington JM. Neurobehavioral effects of long-term occupational exposure to organic solvents: Two comparable studies. Am J Ind Med 1992;22:325-35.

156. Stonard MD, Gore CW, Oliver GJA, Smith IK. Urinary enzymes and protein patterns as indicators of injury to different regions of the kidney. Fumid Appl Toxicol 1987;9:339-51.

157. Stopps GJ, McLaughlin M. Psychophysiological testing of human subjects exposed to solvent vapors. Am Ind Hyg Assoc J 1967;5:43-50.

158. Strobino B, Kline R, Stein Z. Chemical and physical exposure of parents: effects on human reproduction and offspring. Early Hum Dev 1978;1/4:371-99.

159. Stüber K. Health damages at occupational use of trichloroethylene and options for preventive measures. (In German). Arch Gewerbepath Gerwerbehyg 1931;2:398-456.

160. Sucio I, Olinici L. Hepato-renal involvement in acute occupational trichloroethylene intoxication. Med Lav 1983;74:123-8.

161. Söderman E, Kjellberg A, Olson BA, Iregren A. Standardization of simple reaction time for behavioral toxicological studies". (In Swedish). Stockholm: National Institute of Occupational Health, 1982.

162. Torkelson TR, Rowe VK. Halogenated aliphatic hydrocarbons containing chlorine, bromine and iodine. In: Clayton GD, Clayton FE (eds.). Patty's industrial hygiene and toxicology. New York: Wiley Interscience 198;3433-3601.

163. Trense E. Practical results from examinations of 546 TRI-workers. Zbl Arbeitsmed Arbeitsschutz 1965;15:114-6.

164. Triebig G et al. Neurotoxicity of solvent mixtures in spray painters. Int Arch Occup Environ Health 1992;64:361-72.

165. Triebig G, Trautener P, Weltle D, Saure E, Valentin H. Investigations on neurotoxicity of chemical substances at the workplace. (In German). Int Arch Occup Environ Health 1982;51:25-34.

166. Triebig G. Occupational neurotoxicology of organic solvents and solvent mixtures. Neurotox Teratol 1989;11:575-8.

167. Triebig G, Schaller K-H, Erzigkeit H, Valentin H. Biochemical examinations and psychological studies among persons chronically strained by trichloroethylene but with intervals with no exposure. (In German). Int Arch Occup Environ Health 1977;38:149-62.

168. Vainio H, Waters MD, Norppa H. Mutagenicity of selected organic solvents. Scand J Work Environ Health 1985;Suppl. 11:1:75-82.

169. Valciukas JA, Lilis R, Singer RM, Glickman L, Nicholson WJ. Neurobehavioral changes among shipyard painters exposed to solvents. Arch Environ Health 1985;40:47-52.

170. Valciukas JA. Foundations of Environmental and Occupational Neurotoxicology. New York: Van Nostran Reinhold, 1991.

171. Vernon RJ, Ferguson RK. Effects of trichlorothylene on visual-motor performance. Arch Environ Health 1969;18:894-900.

172. Verschoor M, Herber R, Hemmen JV, Wibowo A, Zielhuis R. Renal function of workers with low-level cadmium exposure. Scand J Work Environ Health 1987;13:232-8.

173. Vliet C et al. Exposure-outcome relationships between organic solvent exposure and neuropsychiatric disorders: results from a Dutch case-control study. Am J Ind Med 1989;16:707-18.

174. Ward JB, Hokanson JA, Smith ER, Chang LW, Pereira MA, Wharton EB, Legator MS. Sperm count, morphology and fluorescent body frequency in autopsy service workers exposed to formaldehyde. Mutat Res 1984;130:417-24.

175. Wechsler O. Wechsler Adult Intelligence Scale. Manual. New York: New York Psychological Corporation, 1955.

176. White RF, Feldman RG. Neuropsychological assessment of toxic encephalopathy. Am J Ind Med 1987;11:395-8.

177. White RF, Proctor SP. Research and clinical criteria for development of neuro-behavioral test batteries. J Occup Med 1992;34:140-8.

178. Winneke G. Acute behavioral effects of exposure to some organic solvents - psychophysiological aspects. Acta Neurol Scandinav 1982;66: (suppl. 92):117-29.

179. Wohlert M, Nielsen J, Johansson M. Cytogenetic and occupational medical investigation of 28 laboratory technicians in a research laboratory. Ugeskr Læger 1986;148:578-81. (in Danish).

180. World Health Organization. Laboratory manual for the examination of human semen and semen-cervical mucus interaction. Press Concern, Singapore 1980, pp. 1-43.

181. World Health Organization. Chronic effects of organic solvents on the central nervous system and diagnostic criteria. Environmental Health Series no. 5. WHO Regional Office for Europe, Copenhagen 1985.

182. Yuen C.-T., Price RG, Chattagoon L, Richardson AC, Praill PFG. Colorimetric assays for N-acetyl-beta-D-glucosaminidase and beta-D-galactosidase in human urine using newly-developed ω-nitrostyrol substrates. Clin Chem Acta 1982;124:195-204.

183. Ørbæk P. Effects of long-term exposure to organic solvents on the nervous system. Chronic toxic encephalopathy and the prognosis following cessation of exposure. Malmø: University of Lund, 1987 (thesis).

184. Ödkvist L, Larsby B, Tham R, Hydén D. Vestibulo-oculomotor disturbances caused by industrial solvents. Otolaryngol Head Neck Surg 1983;91:537-9.

185. Weis NS. Cancer in relation to occupational exposure to trichloroethylene. Occup Environ Med 1996; 53:1-5.

Scand J Soc Med 14: 161–168, 1986

Neuropsychological Symptoms among Metal Workers Exposed to Halogenated Hydrocarbons

Kurt Rasmussen and Svend Sabroe

From the Institute of Social Medicine, University of Aarhus, Århus C, Denmark

Neuropsychological symptoms among metal workers exposed to halogenated hydrocarbons. Rasmussen, K. and Sabroe, S. (Institute of Social Medicine, University of Aarhus, Århus, Denmark).

Scand J Soc Med 1986, 3 (161–168).

A cross-sectional study was designed as a questionnaire investigation with the aim of mapping the load of symptoms, especially signs of neuropsychological dysfunction in relation to degreasing with halogenated hydrocarbons. The primary study group, 240 metal workers, comprised all indentifiable persons engaged in degreasing with halogenated hydrocarbons in the county of Aarhus, the control group were 350 randomly selected semi-skilled metal workers. The final number of participants were 462 metal workers, corresponding to a rate of participation of 78.3%. The main findings were highly significant associations between exposure to halogenated hydrocarbons and symptoms of psychological dysfunction both at bivariate and multivariate analyses after adjustment for 4 potential confounder variables, age, alcohol consumption, neurological events and exposure to other organic solvents. Furthermore a dose–response-like relation could be demonstrated.

Keywords: cross-sectional study, epidemiology, neuropsychological dysfunction, metal workers, organic solvents.

Halogenated aliphatic hydrocarbons is a group of organic solvents where the min single substances are: trichloroethylene, 1,1,1-thrichloroethane, methylene chloride, perchloroethylene and fluorocarbons (freons). The four first-mentioned comprise the most used chlorinated solvents. From 1960–70 there was an increase of 350% in the consumption of halogenated hydrocarbons in Denmark (1). In the 1970s there has been a stagnation in consumption analogous with the general stagnation during the current economic crisis.

Halogenated hydrocarbons are used for degreasing within the metal and electronic industries, for chemical dry cleaning, as a substance in glue, as a "blowing agent" within the plastic industries and for a lot of other processes.

In Denmark the metal industries are the branch which consumes the largest quantity of chlorinated solvents, almost exclusively for degreasing and corresponding to 30% of the total consumption of halogenated hydrocarbons.

Trichloroethylene has been in industrial use since 1910, first and foremost for cleaning and degreasing purpose. Health reports related to trichloroethylene exposure have concentrated on trigeminus and peripheral neuropathy, liver damage, affection on cardiac function and a possible cancer risk (2–6). Through the last 10–15 years 1,1,1-trichloroethane and freons have come more extensively into the market, more because of an assumption of lesser toxicity of the products than of technical reasons (2). Through the last decade increasing attention has been paid concerning effects on the central nervous system after long-term exposure to organic solvents. A Danish cohort study has indicated increased risk of early retirement due to presenile dementia (7). Swedish, Danish and Finnish case-referent studies, have indicated that occupational groups with heavy exposure to aromatic and aliphatic hydrocarbons, i.e. construction workers and carpenters/cabinet makers, were granted disability pension as a consequence of neuropsychiatric disorders, twice as often or more than non-exposed workers (8–10). Concerning chlorinated solvents there has been several studies concerning acute effect on psychological performance under climate chamber exposure (11). Exposure to chlorinated solvents is less examined in epidemiological design and the few existing are with inconsistent outcome (12–14).

The object of this study was to map the load of symptoms in relation to work with chlorinated solvents for degreasing of iron works in a population of relatively high- and mono-exposed mainly semi-skilled metal workers.

Table I. *Age distribution in the study group*

Age	Number of persons	%
17–24	87	18.8
25–29	63	13.6
30–34	60	13.0
35–39	53	11.5
40–44	45	9.7
45–49	37	8.0
50–54	49	10.6
55–59	50	10.8
60–64	11	2.4
65+	3	0.6
None-responding	4	0.9
Total	462	100.0
Mean age	37.7	

MATERIAL AND METHODS

The investigation was made in a geographical well-defined area of Eastern Jutland, corresponding to the county of Aarhus, with a population of 600 000 people. All factories with 5 or more employed skilled metal workers, totally 263 plants, were primarily contacted through the shop steward, partly to get information on degreasing products used in each plant, partly to get the name and address of the degreasers—normally 1–3 per plant. With the purpose of identifying all engaged in metal degreasing in this area, we got in addition in contact, through company-lists delivered from the National Labour Inspectorate and chemical companies, with 20 more metal factories which were not found by the first procedure. The wanted information on degreasing was obtained at all 283 plants, and all degreasers working with chlorinated solvents in these plants, were included in the further investigation. At 72 factories we identified 240 degreasers working with chlorinated solvents. Concerning the presently exposed we have in this way probably identified nearly all relevant persons while the exhaustability is less likely for the previously exposed. The control group was 350 metal workers, randomly selected through card files of semi-skilled trade unions in the same geographic area.

All together 590 workers were sampled to participate in the study and they received a self-administered questionnaire in September–November 1982. The questionnaire was returned by 83.8%. 33 persons were excluded owing to job-changes and job-ceasing. Hereafter the final number of participants was 462 metal workers corresponding to a participant rate of 78.3%. The age distribution of the sample population is shown in Table I, average age is 37.7 years, 443 are males and 19 are females. The average age of the different exposure group is given in Table II.

The questionnaire contained 75 questions concerning health and conditions of solvent exposure. The health questions were based on the Swedish "Örebro-questionnaire" (15). In this paper we will concentrate on acute and chronic neuropsychological symptoms as sign of affection on the central nervous system.

Statistical analysis was carried out with the SPSS-programs (16). At small expected values Fisher's exact test has been used, otherwise the chi-square test without correction has been used. The significance of the difference between the three exposure groups and the null-exposure groups was tested by Student's *t*-test and confounder control has been made by logistic regression analysis

Table II. *Number of persons in different exposure groups. Average time of total exposure*

The same persons may work with more than one chlorinated solvent and are therefore able to appear in different places under group A in Table II

Main exposure group	Subgroups	No. of persons	%	Mean age	Average time of total exposure: No. of years	Average time of total exposure: Hours/week
Group A Working with chlorinated solvents presently		171		37.2	7.3	16.5
	Trichloroethylene	97	56.7	36.6	7.2	18.8
	1,1,1-Trichloroethane	64	37.4	37.4	7.6	16.1
	Methylene chloride	11	6.4	37.8	9.5	12.1
	Freon 113	21	12.3	39.3	5.0	13.6
Group B Never worked with organic solvents		94		38.5	0	0
Group C Working only with other organic solvents presently		131		36.7	6.1	12.5
Group D Previously (1–5 years ago) worked with chlorinated or other organic solvents		66		39.6	6.5	14.7

Table III. *Acute and chronic neuropsychological symptoms in the total group exposed to chlorinated solvents compared to the non-exposed control group (%)*

Questions	Control group (group B) $N=94$ % yes	Exposure group (group A) $N=171$ % yes	Relative prevalence proportion Group A/ group B	95% confidence limits	p-value
Do you have headache in relation to your work?	26.1	42.1	1.6	(1.1–2.3)	0.01
Do you suffer from dizziness in relation to your work?	4.3	15.9	3.7	(1.5–9.3)	0.005
Do you have a sensation of drunkenness in relation to your work?	5.4	21.2	3.9	(1.8–8.7)	<0.001
Do you feel abnormally tired?	29.3	48.6	1.7	(1.2–2.3)	0.003
Do you feel that you have become more forgetful?	8.6	26.4	3.1	(1.6–5.8)	<0.001
Do you often go back and check something you have done already, e.g. having locked the door?	11.7	23.6	2.0	(1.1–3.6)	0.02
Do you have difficulty in concentrating?	7.6	18.8	2.4	(1.1–5.0)	0.02
Do you get more easily irritated over minor things than before?	10.6	21.1	2.0	(1.1–3.7)	0.03
Do you get drunk more easily than before?	11.7	20.1	1.7	(0.9–3.2)	0.08
Have your family told you that you have become more irritable?	4.3	16.4	3.8	(1.6–9.6)	0.004

Test of significance: χ^2-test.

where odds ratios have been estimated for the variables forming part of a multiplicative model. Accordance with data (goodness of fit) is controlled with the chi-square-distributed testor G. $G = -2 \ln Q$ where Q is likelihood ratio (17).

RESULTS

The exposure

From information in the questionnaire the material has been divided into different exposure groups whose duration of exposure is shown in Table II. At the time of examination 171 persons (group A) worked with chlorinated solvents when degreasing, or had done so until a year ago, having an average time of exposure of 7.3 years and 16.5 hours a week. Of these 171 workers, the vast majority were exposed to only one chlorinated solvent, most frequently trichloroethylene (57%) and 1,1,1-trichloroethane (37%). 50% were only in contact with chlorinated solvents, and the other 50% were in contact now and then with other organic solvents, mostly petroleum.

The primary group of comparison are 94 persons (group B) who neither at the present time nor previously have ever worked with solvents. These workers are engaged in welding, grinding, stockwork etc. in the same type of metal factories.

Another exposed group are 131 workers (group C) exposed to other organic solvents (petroleum, gasoline, toluene or xylene) when painting, degreasing etc. Also this group has been exposed presently or until a year ago. Finally we have the previously exposed group 1–5 years ago (group D).

In group A the degreasing was done as following: vapour plant 59%, bucket and cloth/brush 36%, open vessel 30%, and closed washing-machine 8%. The 33% of the cases the degreasing apparatus was situated in a separate room. The rest was placed in the production hall together with other machinery. 45% of the degreasers had local air extraction over the working place—55% had not.

Health

In Table III a section of acute and chronic neuropsychological symptoms are shown as an indication of affection of the brain. Headache, dizziness and a sensation of drunkenness is called acute neuropsychological symptoms, while ten symptoms concerning memory and concentration difficulties, irritability, alcohol intolerance and disturbance of sleep are called chronic. These symptoms together with questions concerning fatigue comprise here the neuropsychological symptoms, the main part of

Table IV. *Acute and chronic neuropsychological symptoms in the exposure groups working with different chlorinated solvents compared to the non-exposed control group*

Questions	Control group (group B) $N=94$ % yes	Group A			
		Trichloroethylene $N=97$		1,1,1-trichloroethane $N=64$	
		Relative prevalence proportion	95% confidence limits	Relative prevalence proportion	95% confidence limits
Dizziness	4.3	3.8	(1.5–10.0)	2.9	(1.0–8.7)
Drunkenness	5.4	4.2	(1.8–9.6)	2.4	(0.8–6.7)
Abnormal fatigue	29.3	1.6	(1.1–2.3)	1.8	(1.2–2.6)
Forgetfulness	8.6	2.9	(1.4–5.8)	3.0	(1.4–6.2)
Often go back to check things	11.7	2.3	(1.3–4.3)	2.0	(1.0–4.0)
Difficulty in concentrating	7.6	2.5	(1.1–5.4)	2.3	(1.0–5.5)
Irritability	10.6	2.0	(1.0–4.0)	1.9	(0.9–4.0)
Family complaints of irritability	4.3	3.3	(1.3–9.2)	3.5	(1.1–9.6)

which is significantly more frequent in the group exposed to chlorinated solvents (group A). Compared to group B, only exposed to other organic solvents, we still found excess of symptoms in the chlorinated solvent exposed group, but only in a few questions with significance at the 5% level.

In Table IV we have done the same bivariate analysis in relation to all 4 different chlorinated solvents involved. Trichloroethylene is clearly the substance which causes the most inconveniences and symptoms. Differences are especially great when concerning the acute symptom complex, and we found the 1,1,1-trichloroethane resulted in fewer problems. On the other hand all 4 exposure groups give significant symptoms of chronic affection on the brain.

We have made an exposure index, and the whole group working with chlorinated solvents is divided into 3 exposure groups from a calculation of number of hours' work with degreasing per week, multiplied by number of years of exposure (both pieces of information from the questionnaire) multiplied by 45 weeks per year. This gives an estimation of the total number of exposure hours. The control group which had never worked with solvents at any time is also included here as a zero-exposure group.

Table V. *Prevalence odds ratio of chronic neuropsychological symptoms among metal workers exposed to chlorinated solvents after adjustment for 4 confounding variables by logistic regression analysis*

Response variable: the chronic neuropsychological index of symptoms (positive = ≥4 out of 10 symptoms). $N=365$

Exposure variables	No. of persons	Symptom index		Unadjusted values		Adjusted values[a]	
		Pos.	Neg.	Relative prevalence proportion	95% confidence limits	Prevalence odds ratio	95% confidence limits
Non-exposed	196	26	170	1.0	–	1.0	–
Present exposure to chlorinated solvents—light	54	7	47	0.98	0.45–2.13	0.96	0.38–2.42
Present exposure to chlorinated solvents—medium and heavily	75	25	50	2.51	1.56–4.05	3.42	1.76–6.65
Previous exposure to chlorinated solvents	40	16	24	3.02	1.76–5.16	4.22	1.92–9.26

[a] Adjustment has been made for the following dichotomized confounding variables (adjusted prevalence odds ratio and 95% confidence limits):

Age (dichotomized on 40 years) 0.87 (0.49–1.54)
Alcohol consumption (dichotomized on 3 drinks/day) 2.24 (1.09–4.57)
Cerebral neurological events (no/yes) 1.71 (0.89–3.30)
Exposure to other organic solvents (no/yes) 1.33 (0.76–2.32)

Methylene chloride $N=11$		Freon 113 $N=21$	
Relative prevalence proportion	95% confidence limits	Relative prevalence proportion	95% confidence limits
2.3	(0.3–18.5)	5.5	(1.8–17.0)
6.7	(2.3–19.8)	6.2	(2.4–16.0)
2.2	(1.1–4.2)	1.6	(0.9–2.9)
4.2	(1.5–11.9)	2.8	(1.1–7.6)
2.3	(0.7–7.4)	0.8	(0.2–3.4)
6.0	(2.3–15.4)	1.9	(0.5–6.7)
0.9	(0.1–6.7)	3.2	(1.3–7.3)
6.3	(1.8–22.5)	3.3	(0.9–13.2)

At the same time the number of persons, who to a high degree (yes = yes moderately + yes heavily in the questionnaire) complained of chronic neuropsychological symptoms are counted in each exposure group. This gives an exposure response or dose response-like relation which is shown in Fig. 1. A finding which is fairly unchanged after adjustment for age effect, by direct age standardization, where the total population included in the dose response calculation was used as standard. Furthermore there is statistical significance by comparison of the medium and heavily exposed group to the non-exposed group (group B).

The bivariate analysis has shown highly significant associations between exposure variables and different effect variables, including the chronic neuropsychological symptom index, or individual symptoms of reduction of mental function. A number of risk factors must be considered as being potential confounders of the discovered association. We have found it relevant to adjust for the effect of age, alcohol consumption, cerebral neurological events (cranial traumas with unconsciousness, epilepsy and neuroinfections) and exposure to other organic solvents. The primary exposure variables are *chlorinated solvents presently* (working with chlorinated solvents presently + previously 1–3 months ago—subdivided into a light exposed group and a medium and heavily exposed group) and chlorinated solvents previously, (working with chlorinated solvents previously 3 months to 5 years ago).

The confounder variables have been adjusted for by means of multivariate analyses in the form of logistic regression. The effect variable, what we call the chronic neuropsychological index is the presence of at least 4 out of 10 chronic neuropsychological symptoms (forgetfulness, lack of concentration, irritability etc.).

From the logistic regression analysis in Table V it appears that previous exposure and present medium and heavy exposure to chlorinated solvents, as well as consumption of alcohol are significantly associated with the chronic neuropsychological symptom index. If we compare with unadjusted

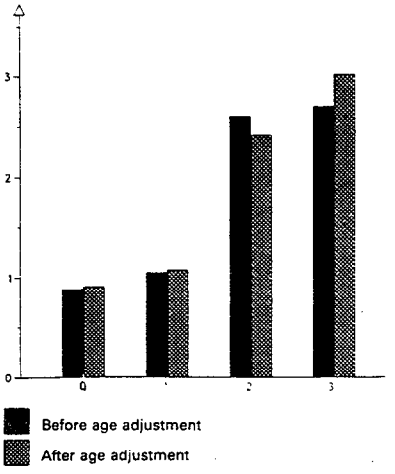


Fig. 1. Dose–response relation. Never worked with organic solvents ($N=94$): Exposure group 0. Working with chlorinated solvents ($N=171$): Exposure group 1–3. Response is mean number of 10 chronic neuropsychological symptoms. Comparison of age-unadjusted symptom values between exposure groups. Test of significance: *t*-test. Exposure group 0 to 1: p-value = 0.62. Exposure group 0 to 2: p-value <0.001. Exposure group 0 to 3: p-value <0.001.

Mean exposure

Exposure group	No. of persons	Mean total exposure
0	94	0 hours
1	63	445.7 hours, e.g. 5 hours per week for 2.0 years
2	55	2 494.6 hours, e.g. 10 hours per week for 5.5 years
3	45	12 841.0 hours, e.g. 40 hours per week for 7.1 years
	8	None-responding

values from bivariate analyses (relative prevalence proportion in Table V) we see a negative confounding, i.e. when the effect of confounding factors are adjusted in a multivariate analysis the relation between explanation variables and the response variable increases.

DISCUSSION

The excess of neuropsychological symptoms in the group of degreasers working with chlorinated solvents is comparable to the findings in other studies of solvent-exposed workers (18, 19). The division into acute and chronic symptoms is not ruled by any convention, but is here made from a toxicological/occupational medical point of view. In this way the division is debatable, e.g. fatigue and alcohol intolerance contain elements of both acute and chronic symptomatology. The most surprising results in the bivariate tables are probably the findings pointing at acute and chronic neurotoxicity after freon exposure. Freons are in the literature generally described as fairly untoxic—the Danish TLV is 500 ppm (20). Freon for metal degreasing is exclusively Freon 113 (1,1,2-trichloroethane, 1,2,2-trifluoroethane). The majority of the freon group in this study is composed by a high-exposed group of degreasers from one factory where the normal consumption of freon has been about 50 litres per week for each degreaser. Correspondingly we have done a few charcoal tube samplings and found time-weighed average concentrations in the breathing zone air in the range of 260–420 ppm. This is an unusually high air concentration of a solvent under nowaday Danish hygienic standard.

The finding of an overfrequency of solvent related symptoms in the group exposed to chlorinated solvents compared to the group exposed to other organic solvents may be reasoned in comparison of two inhomogenous groups. The primary group is probably more total and representative than the group using other organic solvents.

The effect we are measuring, neuropsychological symptoms as a sign of psychological dysfunction and emotional disturbances can be *confounder-biased*. Important confounders are "hard-variables" as age, alcohol consumption, cranial traumas etc. which we have adjusted for. "Soft-variables" as psychosocial factors may also play a role, if they are unevenly distributed among exposed and unexposed. It is probably not the case here, to any determinating degree, as both groups are semi-skilled metal workers, living in the same geographic area, working at the same kind of factories, in several cases even the same one. The job content should not either give rise to bias, the difference concerning monotony and tedious work is probably small between degreasing work and for example welding or clearing work. It is difficult to adjust for this kind of confounders because of difficulty of getting valid measurements of these variables.

Information-bias is always discussable in studies of this type especially after a raised information level through the last 6–8 years, concerning the danger to solvent exposure. The existence of a dose–response relation makes information-bias at any greater level unlikely—a degreaser exposed 1 year 40 hours per week reveals in exposure group 1, but should under influence of information-bias tend to have many complaints and symptoms and thereby spoil the dose–response relationship.

A tendency to emigrate from factories and jobs with hygienic problems under the assumption of health conditions being poorer for those gone than staying, gives possibility to *selection-bias*. The high symptom rate in the previous chlorinated solvent-exposed group in Table V, could give support for this assumption. Primary selective mechanisms are probably ambiguous. Degreasing, often fairly well paid, is normally not considered among the most dirty jobs, but on the other hand it is a fairly simple and unskilled function with a possibility for selection bias concerning intellectual level of the degreasers. The control group is not purely unexposed to neurotoxic agents (e.g. welding fumes), this together with possible secondary healthy worker effect tends to underestimation of the relative risk found. In Denmark metal industries are not concentrated in any special geographic region, our findings from East-Jutland should be assumed to be extendable to the rest of Denmark.

The hypothesis we primarily have wanted to test is the relation: exposure to chlorinated solvents resulting in chronic damage to the central nervous system. Ideally we are interested partly in the frequency and the nature of chronic damage on the central nervous system in general, partly in an illumination of the reversibility of the damage, i.e. determination of the risk of chronic irreversible damage, first and foremost chronic toxic encephalopathy (or chronic psychoorganic syndrome). This result can only be approached in a cross-sectional

design like the present, and of course we cannot diagnose a disease entity like the "psychoorganic syndrome" in a questionnaire.

In Sweden some attempts have been made to validate questionnaires against clinical medically and psychologically diagnosed CNS-effects after solvent exposure. In Örebro in Sweden there has been developed a questionnaire, called "Q16" which contains 16 questions concerning psychological dysfunction and neurological complaints. Q16 has in validation studies been found to have a relatively high sensitivity but a low specificity, in accordance with an important demand to a screening instrument (21). In Sweden Q16 is used in the way that persons under the age of 28 with more than 4 symptoms and persons at or above 28 with more han 6 symptoms have been found screening-positive, which should lead to further investigations, for example a psychological examination. 7 of our 10 chronical neuropsychological questions are identical to the questions in the Swedish questionnaire. If we in the actual study use the relatively restrictive criterion like the presence of more than 6 of 10 chronic neuropsychological symptoms 16 persons from the exposed group (group A) compared to 1 person from the control group (group B) should be referred to further clinical examination.

The conclusion from this study is, that a highly significant association has been shown between exposure to chlorinated solvents and symptoms of psychological dysfunction at bivariate analyses and a dose–response relation. At multivariate analyses there was found a highly significant association between exposure and response, adjusted for the effect of potential confounders. Signs of chronic irreversible symptoms have been found in the group previously exposed to chlorinated solvents. The exposure background for this is that manual degreasing without or with insufficient local air extraction is still very wide-spread in the metal industries.

ACKNOWLEDGEMENT

This work was supported by grants from Sygekassernes Helsefond.

REFERENCES

1. Mikkelsen AB, Petersen R, Rasmussen K, Sabroe S. Klorerede opløsningsmidler—et arbejdsmiljøproblem. Copenhagen: Munksgård, 1983.
2. Aviado DM, Zakhari S, Simaan IA, Ulsamer AG. Methylchloroform and trichloroethylene in the environment. Cleveland, Ohio: CRC Press, 1976.
3. Dimitrova M, Usheva G, Pavlova S. The work environment's influence on the cardiovascular system. Polycardiographic investigations in workers exposed to trichloroethylene. Int Arch Arbeitsmed 1974; 32: 145–8.
4. Feldman RG, Mayer RM, Taub A. Evidence for peripheral neurotoxic effects of trichloroethylene. Neurology 1970; 20: 599–606.
5. Huff JE. New evidence of the old problems of trichloroethylene. Industr Med 1971; 40: 25–33.
6. National Institute for Occupational Safety and Health. Trichloroethylene. Rockville, Maryland, 1975, NIOSH (Current Intelligence Bulletin 2).
7. Mikkelsen S. A cohort study of disability pension and death among painters with special regard to disabling presenile dementia as an occupational disease. Scand J Soc Med 1980; Suppl 16: 34–43.
8. Axelson O, Hane M, Hogstedt C. A case-referent study on neuropsychiatric disorders among workers exposed to solvents. Scand J Work Environ Health 1976; 2: 14–20.
9. Lindström K, Riikimäki A, Hänninen K. Occupational solvent exposure and neuropsychiatric disorders. Scand J Work Environ Health 1984; 10: 321–3.
10. Sabroe S, Olsen J. Health complaints and work conditions among lacquerers in the Danish furniture industry. Scand J Soc Med 1979; 7: 97–104.
11. Aastrand I, Kilbom AA, Wahlberg I, Övrum P. Exposure to methylchloroform. Arbetarskyddsverket, Stockholm, 1972. (Arbete och Hälsa 1972: 1.)
12. Lilis R, Stanesen D, Muica N, Roventa A. Chronic effects of trichloroethylene exposure. Med Lavaro 1969; 60: 595–601.
13. Okta T, Nakamura H, Itani J, Itani T, Ogawa T, Aoyama H. A study on the intoxication of methylchloroform workers. J Science Lab 1979; 55: 215–20.
14. Triebig G, Schaller KH, Erzigkeit H, Valentin H. Biochemische Untersuchungen und psychologische Studien an chronisch trichloräthylenbelasteten Personen unter Berücksichtigung expositionsfreier Intervalle. Int Arch Occup Environ Health 1977; 38: 149–62.
15. Axelson O (ed.). Responsregistrering vid lösningsmedelsexposition. Synpunkter från ett nordiskt arbetsmöte i Örebro 15–16 April 1975. Stencil. Örebro, Sverige, 1975.
16. Nie NH, Hull CH, Jenkins JG, Steinbrenner K, Bent DH. Statistical package for social sciences. New York: McGraw-Hill, 1975.
17. Breslow NE, Day NE. Statistical methods in cancer research. Lyon, 1980 (IARC Scientific publications no. 32).
18. Hane M, Hogstedt C, Sundell L. Frågeformulär om neuropsykiatriska symptom för hälsokontroll vid lösningsmedelexposition. Läkartidningen 1980; 77: 437–9.
19. Olsen J, Sabroe S. A case-referent study of neuropsychiatric disorders among workers exposed to solvent in the Danish wood and furniture industry. Scand J Soc Med 1980; Suppl 16: 44–9.

20. Edling C, Söderkvist P. Criteria document for Swedish occupational standar. Fluorocarbons. Arbetarskyddsverket, Stockholm, 1982. (Arbete och Hälsa 1982: 26.)
21. Hogstedt C, Anderson K, Hane M. A questionnaire approach to the monitoring of early disturbances in central nervous functions. In: Aito A, Riikimäki V, Vainio H, eds. Biological monitoring and surveillance of workers exposed to chemicals. Washington: Hemisphere Publishing Corporation, 1984: 275–87.

Address for offprints:

Dr K. Rasmussen
Institute of Social Medicine
University of Aarhus
Vesterbro Torv 1–3, 6.
8000 Århus C
Denmark

American Journal of Industrial Medicine 23:779–792 (1993)

Solvent-Induced Chronic Toxic Encephalopathy

Kurt Rasmussen, MD, Hans Jeppe Jeppesen, MSc, and Svend Sabroe, MD

Chlorinated solvents, especially trichloroethylene, have been extensively used for metal degreasing since the beginning of this century. There have been case reports of cranial nerve damage and symptoms of acute and reversible encephalopathy. However, another issue during the last decade is the possible existence of a syndrome of chronic cerebral dysfunction. Our study deals with the risk of developing a state of psychoorganic syndrome after long-term exposure to solvents, mainly trichloroethylene. In this historical cohort study, 96 metal degreasers participated in a clinical medical and psychological examination. The risk of developing psychoorganic syndrome was proportional to the exposure duration, to increasing age, and to decreasing primary intellectual level. Using logistic regression analysis, there was a significantly increased risk of developing psychoorganic syndrome from solvent exposure. There was an odds ratio of 5.6 (0.93–34.3) for psychoorganic syndrome in the medium-exposed group. In the most highly exposed group, with a mean full-time exposure duration of 11 years, there was a significantly increased risk of psychoorganic syndrome, the adjusted odds ratio was 11.2 (1.9–66.6). None of four other potential confounders (arteriosclerotic disease, neurologic/psychiatric disease, alcohol abuse, and current solvent exposure) had any significant associations to psychoorganic syndrome.

Key words: chlorinated solvents, trichloroethylene, neurotoxicity, psychoorganic syndrome

INTRODUCTION

Chlorinated hydrocarbon solvents have been widely used as degreasing agents in the metal industry and as solvents for organic products since about 1910, with trichloroethylene as the predominant product through most of the period. Since the mid-1970s the total use of chlorinated solvents has slowed, and there has been a gradual substitution from trichloroethylene to products evaluated as less toxic, such as 1,1,1-trichloroethane and the halogenated product 1,1,2-trichloro-1,2,2-trifluoroethane (CFC 113), yet the number of workers daily or frequently exposed to trichloroethylene is 3,500,000 in the United States and 5,000 in Denmark.

Through the last two decades, increasing attention has been paid to the relationship between long-term solvent exposure and chronic brain dysfunction. A modest, but consistent etiologic association was found in three Scandinavian case-referent

Institute of Epidemiology and Social Medicine (K.R., S.S.) and Department of Occupational Medicine (H.J.J.), University of Aarhus, Aarhus, Denmark.
Address reprint requests to Kurt Rasmussen, Department of Occupational Medicine, Herning Hospital, DK-7400 Herning, Denmark.
Accepted for publication June 11, 1992.

studies [Axelsson et al., 1976; Olsen and Sabroe, 1980; Lindström et al., 1984] and lately confirmed in a U.S. study [Brackbill et al., 1990]. In a Danish study based on a clinical analysis of a historical cohort of painters, compared with a control group of bricklayers, significant relative risks of 3.5–5.0 for dementia in the medium-exposed and highly exposed groups were found [Mikkelsen et al., 1988]. Studies outside Scandinavia, mainly cross-sectional clinical studies, have not supplied convincing evidence to support the hypothesis of solvent exposure causing irreversible brain damage [Fidler et al., 1987; Triebig et al., 1989]. The reason for this discrepancy might lie in differences of study design, incomparable study populations, insufficient adjustment for confounding factors, and, perhaps most importantly, differences in disease classification.

Soon after the introduction of trichloroethylene into German industry as a degreasing agent during World War I, there were reports of neurological manifestations related to exposure [Plesner, 1915]. Since then, there have been current case histories on cranial nerve disturbance or fatal cases with severe histological alterations in the central nervous system after accidental overexposure or degreasing inside a tank [Mitchell and Parssons-Smith, 1969; Feldman et al., 1985]. From the 1950s to the 1970s, there have been several reports on neuropsychological symptoms called *neurosis* or *psychoorganic syndrome* among industrial cohorts. These studies were performed without control for confounding factors [Grandjean et al., 1955; Lilis et al., 1969].

More recent studies have given epidemiological support to the evidence of disturbances of cranial and peripheral nerve function after occupational exposure to trichloroethylene under nonaccidental circumstances [Barret et al., 1984; Ruijten et al., 1991], although the reports are not consistent [Triebig et al., 1982]. There has been sparse and nonconclusive follow-up of the issue of chronic diffuse brain damage after long-term exposure to trichloroethylene [Triebig et al., 1977; Rasmussen and Sabroe, 1986].

Our study population of metal degreasers has been exposed mainly to trichloroethylene. However, the study dealt with health effects after cumulative exposure through a working life, and most of the population were exposed to other solvents, whose effect on the central nervous system could not be separated from that of trichloroethylene. The purpose of this study was to examine the association between long-term occupational exposure to degreasing solvents, and the degree of psychoorganic syndrome as a sign of organic brain damage, through a study design and analysis intended to minimize confounding.

MATERIALS AND METHODS

Study Population and Health Assessment

The investigation was undertaken in the county of Aarhus, Denmark, where approximately 600,000 persons live in an industrial region of small and medium-sized plants. All factories with five or more metal workers, a total of 263 plants, were initially contacted to obtain data on degreasers and degreasing products. At 72 factories, we identified 240 degreasers working with chlorinated solvents.

From this study population of all identifiable metal degreasers in 1982, all workers who had degreased using either trichloroethylene or fluorocarbon (CFC 113) were selected for a 1-day clinical medical examination in a hospital department of

occupational medicine; 116 degreasers fulfilled the exposure criteria. The clinical study was undertaken in 1984–1985. The study design is a follow-up study in a historical cohort of metal degreasers from 1982.

Of 116 persons eligible, 16 declined to participate, and one had died. The total number of participants was 99 persons, a participation rate of 85.3%. The age range was 19–68 years, mean age 39.4 years; 90 were males, nine were females. At the time of investigation 81 workers were employed; nine were unemployed; four were on sick leave; and five had retired, four because of age and one because of illness.

There was no external control group. However, since all degreasers who fulfilled the criteria are included, and the range of full time degreasing was from 1 month to 36 years, internal comparison groups could be established.

The examination of each subject consisted of a medical interview, a clinical neurological examination, a neuropsychological examination, and blood and urine laboratory tests including biological monitoring for trichloroethylene and its metabolites. The medical interview included questions on lifelong exposure and disease. The psychological examination consisted of performance in tests of intellectual impairment and a clinical observation of behavior and cooperation during the examination. The psychological examination was performed under a blind procedure, where the psychologist had no knowledge of occupational exposure or the medical data. However, the physician was not blinded to exposure when assessing symptoms. The medical and psychological examinations lasted approximately 2 hr each and were all performed by the same medical doctor and the same psychologist. The final assessment of the degree of psychoorganic syndrome was made by the two clinical investigators together, based on integrated information of the history of symptoms of mental impairment, performance in psychometric tests, and clinical signs of demential behavior, including an evaluation of how the subject handled the test situation. The test battery consisted of subtests from WAIS and Luria in combination with tests developed in Finland, Sweden, and Denmark in the context of occupational medicine [Rasmussen et al., in press].

The psychometric tests used were WAIS vocabulary in the original WAIS version; simple reaction time; acoustic-motor function; discriminatory attention; sentence repetition (revised Benton); PASAT; Digit span; Text Repetition; Rey's auditory verbal learning; visual gestalts; stone pictures; the digit symbol test from WAIS; revised Santa Anna Dexterity; motor function ad modum Luria; Mira (psychomotor ability without optical control). All are well-known general psychometric tests [Christensen, 1974; Hänninen et al., 1976; Lezak, 1983; Hartman, 1988], except stone pictures, a visual memory test developed for this investigation. In this test, black-white slides of ten stones of different size and shape were shown; the task was to identify ten stones among 25 slide-presented stones, immediately afterwards and after 1 hr. As a nonvalidated test, the stone picture test was tested as a comparison with the other well-known visual learning and retention tests.

The principal outcome variable of this study was psychoorganic syndrome, a mild syndrome of dementia characterized by cognitive impairment, personality changes, and reduced motivation, vigilance, and initiative. The diagnosis requires a characteristic symptom pattern and neuropsychological test results. The degree of psychoorganic syndrome (demential score) was grouped in "no," "suspect," "mild," "mild to moderate," "moderate," "moderate to severe," and "severe." As "suspect" were those considered with a heavy load of neuropsychological com-

TABLE I. Cumulative Exposure to Organic Solvents Among Metal Degreasing Workers: 2.5 Years Follow-Up

	Exposure groups		
	Low (n = 19)	Medium (n = 36)	High (n = 41)
No. of hours of exposure (range)	90–1,639	1,640–6,999	7,000–64,125
No. of years with full time exposure (mean)	0.5	2.1	11.0

plaints but reduced performance only in a few psychological tests, corresponding to a stage between type 1 and type 2A according to the WHO criteria. The categories "mild" and "mild to moderate" comprised broadly reduced test performance corresponding to type 2B and type 3, respectively, of the WHO criteria. No cases of psychoorganic syndrome more severe than "mild to moderate" were found.

For two immigrants, the verbal tests were found invalid because of problems with the Danish language, and, in one case, the test was incomplete because of technical problems with the test machinery. Thus, this analysis reports on 96 metal workers exposed to solvents.

Exposure Assessment

Metal degreasing was done with pure solvent, either in a vapor plant or as cold degreasing with a cloth/brush in an open vessel or in a bucket. A few bigger plants used a closed washing machine.

A detailed lifelong occupational history was taken with information of types of solvents used in number of hours per week and number of years, together with general hygienic working conditions. The criteria for inclusion were intended to create a group of workers singly exposed either to trichloroethylene or to CFC 113. However, in studying chronic toxic encephalopathy, the relevant exposure measurement is the lifelong cumulative exposure. Some had previously degreased using aliphatic solvents such as thinner or white spirit, whereas only a few had previously been industrial painters.

A cumulative exposure index was calculated using number of hours of work with degreasing or other direct solvent exposure per week, multiplied by the number of years of exposure, multiplied by 45 working weeks per year. From this estimation of the total number of exposure hours, three exposure groups were established, with mean years of full-time solvent exposure of 0.5 year and 2.1 and 11.0 years, respectively (Table I).

The dominant exposure for 70 workers was trichloroethylene with a mean exposure time of 7.1 years, 25.0 hours per week; for one person, the exposure was aromatic hydrocarbons with trichloroethylene as additional exposure; for 25 persons, CFC 113 was the dominant exposure, with mean exposure time of 4.2 years and 15.1 hours per week. Current or recent exposure to trichloroethylene was quantified by blood and urine analyses of the metabolites trichloroacetic acid (TCA) and trichloroethanol (TCE). The mean urine TCA in the highest exposure group was 7.7 mg/liter, with a maximum TCA of 26.1 mg/liter. There have not been any systematic air measurements through the long relevant exposure period. However, parallel to the present study, we have evaluated historical exposure data after exposure to trichlo-

roethylene by reviewing all measurements of TCA in urine that were reported to the Danish Labour Inspection Service during the period 1947–1987 [Christensen and Rasmussen, 1990]. From the mid-1950s to the mid-1970s, the Danish exposure level seems to have been fairly constant, corresponding to about 40–60 mg/liter urine TCA. Before that, the exposure level was higher, then rapidly declining after the late 1970s.

Twenty-three of the 25 CFC exposed workers came from a single large textile plant where degreasing of spinning machines with pure CFC 113 was done with the liquid solvent poured into a 1-liter jug and applied with a brush. There was no ventilation system. The weekly usage per worker in this CFC cleaning was approximately 40–65 liters. Measurements of the work environment at this plant showed time-weighted average concentrations in the breathing zone of 260–420 ppm; the U.S. TLV and the corresponding Danish guiding hygienic limit value is 500 ppm.

Confounders

The following variables were considered as potential competing risk factors for the diagnosed psychoorganic syndrome: age, primary intellectual level, history of arteriosclerotic disease, history of neurological/psychiatric disease, alcohol abuse, and current exposure to organic solvents. The distribution of these confounding variables in relation to the outcome variable, and the level of solvent exposure, is shown in Tables II and III.

When studying the relation between *age* and psychoorganic syndrome, using age as a continuous variable, one would assume a linear relation. Biological plausibility, however, would indicate an S-shaped relation. Initial analysis by 10-year age groups showed 40 years as an inflection point, with a high degree of association at 40+ years. This is the rationale behind the three age groups in the confounder analysis.

The test performance in WAIS vocabulary, a test assumed to be resistant to the effects of organic brain damage, was used to estimate *primary intellectual level* [Lezak, 1983; Mikkelsen et al., 1988]. The age standardized scale score, after the U.S. standardization of age adjustment, was used [Wechsler, 1955].

The dichotomous variable *arteriosclerotic disease* was positive for those with a history or current symptoms or objective signs of systemic arteriosclerosis. This included 14 persons with intermittent claudication, angina pectoris, acute myocardial infarction, or electrocardiographic signs of coronary arteriosclerosis. None of the subjects had anamnestic information on stroke or transient cerebral ischemia.

Considered as subjects with relevant neurologic disease were five persons with postconcussional symptoms lasting more than 3 months and one with former light grand mal epilepsy; none had a history of neuroinfections. These six persons, together with four persons with former primary psychiatric disease of depressive character (two of them under present psychopharmacological treatment), and one person with mental retardation, were given a positive value for a confounder variable designated *neurological/psychiatric disease*.

Alcohol abuse was recorded as an average weekly reported consumption of more than 21 drinks per week or a history of alcoholism, defined as periods with treatment for alcohol abuse; five persons fulfilled these criteria.

Finally, we were interested in the effect of long-term exposure in contrast to

TABLE II. Distribution of Potential Confounders in Relation to Psychoorganic Syndrome in 96 Metal Degreasing Workers Followed for 2.5 Years

Confounding variables		Psycho-organic syndrome (n = 42)		No psycho-organic syndrome (n = 54)		Total (n = 96)		p value[a]
		n	Percent	n	Percent	n	Percent	
Binary								
Arteriosclerotic	Yes	9	21.4	5	9.3	14	14.6	
disease	No	33	78.6	49	90.7	82	85.4	0.14
Neurological/								
psychiatric	Yes	6	14.3	5	9.3	11	11.5	
disease	No	36	85.7	49	90.7	85	88.5	0.53
Alcohol abuse	Yes	2	4.8	3	5.6	5	5.2	
	No	40	95.2	51	94.4	91	94.8	1.00
Present solvent	Yes	22	52.4	29	53.7	51	53.1	
exposure	No	20	47.6	25	46.3	45	46.9	0.90
Scaled								
Age								
≤ 29 years		4	16.7	20	37.0	24	25.0	
30–39 years		7	26.9	19	35.2	26	27.1	<0.01
40+ years		31	67.4	15	27.8	46	47.9	
		Psychoorganic syndrome (n = 42)		No psychoorganic syndrome (n = 54)				
		Mean	SD	Mean	SD			
Continuous								
Primary intel-lectual function (WAIS voca-bulary)		12.1	1.6	12.6	1.8			0.19

[a]The p values are from Fisher's exact test for binary variables, χ^2 trend test for scaled variables, and a t test for continuous variables.

acute neurotoxic impairment. Thus, *current solvent exposure* was recorded as a confounder, 53 subjects having been exposed through the last month.

Statistical Analysis

Tests of significance included Fisher's exact test, χ^2 trend test, t test, and analysis of variance. Confounder adjustment was made by logistic regression analysis where odds ratios were estimated by the variables forming part of a multiplicative model. Goodness of fit was controlled with the χ^2 distributed tester. G. $G = -2 \ln Q$, where Q is the likelihood ratio [Breslow and Day, 1980].

RESULTS

The distribution of degrees of psychoorganic syndrome by solvent exposure levels is shown in Table IV. Among metal degreasers, the prevalence of mild or more than mild psychoorganic syndrome was 10.5% for those with low exposure category, 38.9% for medium exposure, and 63.4% for high exposure. Of the 42 persons with

TABLE III. Distribution of Potential Confounders in Relation to Cumulative Solvent Exposure Level (n = 96)

Confounding variables		Exposure groups: Low (n = 19) n	Low (n = 19) Percent	Medium (n = 36) n	Medium (n = 36) Percent	High (n = 41) n	High (n = 41) Percent	Total (n = 96) n	Total (n = 96) Percent	p value[a]
Binary										
Arterioscle-	Yes	2	10.5	2	5.6	10	24.4	14	14.6	
rotic disease	No	17	89.5	34	94.4	31	75.6	82	85.4	0.07
Neurological/	Yes	2	10.5	5	13.9	4	9.8	11	11.5	
psychiatric disease	No	17	89.5	31	86.1	37	90.2	85	88.5	0.87
Alcohol	Yes	1	5.3	2	5.6	2	4.9	5	5.2	
abuse	No	18	94.7	34	94.4	39	95.1	91	94.8	0.93
Present solvent	Yes	10	52.6	22	61.1	19	46.3	51	53.1	
exposure	No	9	47.3	14	38.9	22	53.7	45	46.9	0.47
Scaled										
≤29 years		7	36.8	14	38.9	3	7.3	24	25.0	
30–39 years		7	36.8	9	25.0	10	24.4	26	27.1	0.10
40+ years		5	26.4	13	36.1	28	68.3	46	47.9	<0.0001
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Continuous										
Primary intellectual function (WAIS vocabulary)		12.6	1.5	11.9	1.7	12.7	1.8	12.4	1.7	0.12

[a]The p values are from χ^2 trend analysis. For age, the group ≤29 years is used as reference against the two other groups in the analysis. For primary intellectual function an analysis of variance is used as test of homogeneity for the distribution of confounders on exposure groups and the p value is an expression of the between-group variability.

TABLE IV. Frequency of Psychoorganic Syndrome in Three Exposure Groups of Metal Degreasers by Cumulative Exposure to Organic Solvents (n = 96)[a]

Degree of psychoorganic syndrome	Exposure level: Low (n = 19) n	Low (n = 19) Percent	Medium (n = 36) n	Medium (n = 36) Percent	High (n = 41) n	High (n = 41) Percent
No psychoorganic syndrome	13	68.4	7	19.4	5	12.2
Suspected	4	21.1	15	41.7	10	24.4
Mild	2	10.5	11	30.6	18	43.9
Mild to moderate	0	—	3	8.3	8	19.5

[a]χ^2 trend analysis: low vs. medium exposure $\chi^2 = 11.0$, p value < 0.001; low vs. high exposure $\chi^2 = 19.6$, p value < 0.001

psychoorganic syndrome, 31 had been predominantly exposed to trichloroethylene and seven had exclusively been exposed to trichloroethylene. Of 25 persons exposed to fluorocarbon, eight had psychoorganic syndrome; three had exclusively been exposed to CFC. The data do not allow more specific conclusions about the dementia-

inducing potential of single solvents. The predominant exposures were trichloroethylene and CFC 113, but many of the workers also had some additional lifetime exposure to aliphatic or aromatic hydrocarbons.

From the logistic regression analysis shown in Table V, it appears that there was an increased risk of developing psychoorganic syndrome after solvent exposure. After adjustment for potential confounders, however, the association was significant only for the highest exposed group, who had an average full time exposure of 11 years. The risk of psychoorganic syndrome increased significantly with increasing age and decreasing performance in the WAIS vocabulary test, used as a proxy variable for primary intellectual function. None of the other potential confounders had any significant effects on the risk of developing psychoorganic syndrome. These conclusions can be drawn from model III in Table V, which gives adjusted odds ratio for the independent variable and all confounder variables included in the multivariate analysis.

This study group had an age distribution from 19 to 68 years. Age is strongly correlated with cumulative exposure. None of the younger subjects had any possibility of being categorized as highly exposed, so age adjustment relied on the relatively few old workers with low cumulative exposure. Model I in Table V shows the effect of solvent exposure adjusted only by age; a marked fall in odds ratio from 14.7 to 9.3 after adjustment for age is seen in the most highly exposed groups. The role of the predominant confounder, age, was ruled out by analysis of interaction. No interaction was found, so the actions of age and solvent exposure in relation to psychoorganic syndrome are conceptually independent. The effects of age and high solvent exposure in this study are found to be of about the same magnitude (Table V).

Adjustment by WAIS vocabulary is the opposite of age because of a fairly strong contradictory relation between dementia and performance in WAIS vocabulary; i.e., a high vocabulary score was negatively associated with dementia but positively with age. Model II in Table V gives the odds ratios with only age and WAIS vocabulary included as confounders.

DISCUSSION

This study shows that the risk of developing psychoorganic syndrome was associated with long-term solvent exposure. The diagnosis of psychoorganic syndrome was primarily based on relevant symptoms (increased fatigue, memory impairment, difficulties in concentration, personality changes such as passivity) and reduced psychometric test performance. The score of psychoorganic syndrome was also associated with increasing age and lower preexposure intellectual level. However, the effect of solvent exposure was significant, when the effects of age and preexposure intellectual level were adjusted for in the analyses. The risk of developing psychoorganic syndrome was proportional to the exposure level, but, due to the small number of participants, it was found to be significant only among the most highly exposed, with a mean exposure of 11 years of full-time exposure, ranging from 3.9 to 35.6 years. The relation between sex and psychoorganic syndrome was 40/87, 46% men, and 2/9, 22% women, with psychoorganic syndrome. There was only a small difference in duration of solvent exposure with a mean and range of 6.4 (0.3–16.8) years of life-time exposure for women and 5.4 (0.1–35.6) years for men. The observed difference of the relationship between sex and psychoorganic syn-

TABLE V. Risk of Psychoorganic Syndrome Associated With Cumulative Solvent Exposure After Adjustment for Six Confounding Variables by Logistic Regression Analysis*

	Unadjusted values		Adjusted values					
			Model I		Model II		Model III	
Variables	Odds ratio	95% Confidence interval	Odds ratio	95% Confidence interval	Odds ratio	95% Confidence interval	Odds ratio	95% Confidence interval
Solvent exposure								
Low	1.0	—	1.0	—	1.0	—	1.0	—
Medium	5.4	1.1–27.1	5.8	1.1–32.1	5.6	0.93–34.3	5.9	0.87–39.5
High	14.7	3.0–72.8	9.3	1.7–50.0	11.2	1.9–66.6	13.7	2.0–92.9
Age								
≤29 years	1.0	—	1.0	—	1.0	—	1.0	—
30–39 years	1.8	0.46–7.3	1.6	0.37–6.9	2.0	0.4–9.2	1.9	03.8–9.4
40+ years	10.3	3.0–35.6	7.6	2.0–29.2	16.1	3.4–77.2	19.0	3.5–102.7
Primary intellectual level (WAIS vocabulary)	0.85	0.67–1.1	—	—	0.62	0.45–0.87	0.61	0.43–0.86
Arteriosclerotic disease	2.7	0.82–8.7	—	—	—	—	0.57	0.12–2.8
Neurological/ psychiatric disease	1.6	0.46–5.8	—	—	—	—	2.4	0.48–12.3
Alcohol abuse	0.85	0.14–5.3	—	—	—	—	0.93	0.10–9.0
Present solvent exposure	0.95	0.42–2.1	—	—	—	—	1.1	0.38–3.4

*To show the marked effect of age and primary intellectual level, the odds ratio of the three most important steps of the analysis is presented, model I–III (n=96). Low solvent exposure was used as reference.

drome, which was not statistically significant (Fisher's test $p = 0.16$), may be due to chance.

These results correspond well with findings in a recent Danish investigation [Mikkelsen et al., 1988] based on solvent-exposed house painters and nonexposed bricklayers in a design much like that used in the present study design, and in a few other studies with homogeneous long-term exposed populations. This discussion will be extended below, but first we will make some comments on the validity of this study.

The score of psychoorganic syndrome was intended to measure an acquired mental impairment related to organic brain damage. The measured effect, based mostly on psychological test scoring, can be caused by other factors and the results thereby confounded. The possibility of obtaining valid information on confounding variables is relatively good in a clinical study where a thorough recall interview can be done and objective examinations carried out.

However, some errors may exist in the observed influence of potential confounders. The recorded alcohol habits had no significant relation to psychoorganic syndrome. The reason may be difficulty in getting true and precise information on the amount of alcohol used, resulting in a false-negative effect of the alcohol variable. Also, arteriosclerotic disease and neurological/psychiatric disease were not significantly associated with psychoorganic syndrome. Here, a possible explanation is the small number of subjects with these diseases, in combination with a weak effect. For arteriosclerosis, the weak effect might be due to inclusion of signs and symptoms of systemic arteriosclerotic disease, i.e., without relevance for our actual interest in cerebral arteriosclerosis. Current solvent exposure, including cessation within the last month, was not associated with psychoorganic syndrome. The explanation may be that this group includes a relatively large number of low exposure workers, both currently and on cumulative basis.

However, the score of psychoorganic syndrome was related to age and primary intellectual function. Statistical analyses indicated that age and primary intellectual level were insufficiently adjusted by the age-standardized scale score and not adequately considered in the final clinical interpretation of test performance in the single elements in the score of psychoorganic syndrome. The general validity of this finding concerning primary intellectual function might be limited by the use of only a single test, the WAIS vocabulary, as a proxy variable for primary intellectual function. The WAIS vocabulary has been shown to be sensitive to the effects of lead exposure but resistant to the effects of solvents [Baker et al., 1985; Mikkelsen et al., 1988]. The presumption of WAIS vocabulary being insensitive to cumulative solvent exposure is confirmed in the present study (Table III). The consequence of the above-mentioned systematic error in the scoring of psychoorganic syndrome would be an overestimation of mental impairment in subjects with a low WAIS vocabulary score, and of older age and vice versa, i.e., an underestimation of mental impairment in subjects with high WAIS vocabulary score and of younger age.

Information bias is always possible in studies of this type, especially after an increased awareness of information through the last 10 years about the dangers of solvent exposure. However, the existence of a marked dose-response relationship makes information bias unlikely.

A tendency to abandon factories and jobs with hygienic problems under the assumption that health conditions were poorer for those leaving than for those stay-

ing, gives generally a possibility of selection bias. It didn't take place in this study, but the short follow-up period for this historical cohort from 1982 to 1984–1985, i.e., 2.5 years, does not give sufficient guarantee for control of secondary healthy worker selection. However, such a selection bias would have underestimated the observed relationship between solvents and psychoorganic syndrome.

The present study was not designed to solve questions of whether the brain damage is of diffuse or more focal nature. However, after psychometric testing and neuropsychological examination, the main finding was a broad neuropsychological dysfunction that affected learning, memory, and psychomotor function. Other areas such as verbal performance and motor function were less affected.

It is well-known from a number of cross-sectional studies that solvents give rise to high frequencies of neuropsychological complaints [Hänninen et al., 1976; Hane et al., 1977] and, in some degree, to reduced psychological test performance [Ørbæk et al., 1985]. These findings were first reported from Scandinavian countries but in later years also from other Western countries [Maizlish et al., 1985; Valciukas et al., 1985; Fidler et al., 1987; Triebig, 1989], although generally with more inconsistent findings and lower prevalences and odds ratios. As an explanation for the differences between Scandinavian and other findings, it must be pointed out that the Scandinavian study groups are more uniform and have higher rates of participation. Another factor of importance may be different diagnostic criteria, especially concerning the clinical evaluation of neuropsychological test performance. Generally, in a cross-sectional design, there are difficulties in separating acute from chronic neurotoxic effects as well as difficulties of proper control of other crucial confounding factors. Furthermore, the bias problem related to healthy worker selection is difficult to handle in cross-sectional studies.

The critical issue in solvent toxicity is whether exposed workers run an increased risk of suffering permanent brain damage with irreversible neuropsychiatric brain disease. The studies traditionally considered to indicate a causal relationship between solvent exposure and psychoorganic syndrome or dementia are five Scandinavian studies, four of them case-referent in design [Axelsson et al., 1976; Olsen and Sabroe, 1980; Lindström et al., 1984; Rasmussen et al., 1985] and one a historical cohort-study [Mikkelsen, 1980]. These studies dealt primarily with house painters, and the relative risk estimates were about 2–3 for being disability pensioned with a neuropsychiatric disease or referred to a geriatric ward with a diagnosis of dementia.

The register-based studies outside Scandinavia have reported nonsignificant or low-risk relationships between solvent exposure and dementia [O'Flynn et al., 1987; Gubéran et al., 1989]. However, a recently reported U.S. study [Brackbill et al., 1990] has provided additional evidence using the same design as the four above-mentioned Scandinavian pension studies; it found a significant overall odds ratio of 1.4 for chronic neuropsychiatric disabling conditions among workers previously employed as painters.

Since the industrial introduction of trichloroethylene in the beginning of this century, there have been reports of chronic neurotoxicity. As early as 1931, Stüber [1931] described functional neurosis as a part of chronic intoxication among 82 cases. From the 1950s and 1960s, there have been several human studies on neurobehavioral toxicity. Main findings include high prevalences of neuropsychological complaints, characterized as slight or moderate "psychoorganic syndrome" [Grandjean et al.,

1955; Anderson, 1957; Trense, 1965; Lilis et al., 1969; Smith, 1970]. Unfortunately, these studies had no control groups or adjustment of confounding factors. The survey of Grandjean et al. [1955] resembles the current study in terms of study sampling and exposure. A dose-response relationship was demonstrated between duration of exposure and both neuropsychological symptoms and a psychoorganic syndrome characterized by diminution of memory [Grandjean et al., 1955]. More recent studies have included psychometric tests but had a limited number of study participants [Triebig et al., 1977] or put more focus on the neurological than on the neuropsychological aspects [Barret et al., 1984]. Here, the findings were more diffuse and difficult to interpret. As stated in certain reviews, there are few epidemiological studies of worker populations exposed to trichloroethylene [Annau, 1981; Spencer and Schaumburg, 1985].

In view of the long history of reports of trichloroethylene neuropathy, it is striking that the neurobehavioral literature on the toxic effects of trichloroethylene is still so fragmented and poorly documented. More work is needed to understand the potential toxicity of this compound. However, the present study suggests chronic cerebral dysfunction after long-term exposure to trichloroethylene.

Further studies on the causal relationship between solvent exposure and dementia should be in the design of historical cohort studies, as recommended by the latest international solvent conference [Arlien-Søborg, 1991]. At this conference, future research needs were found to be standardization of neuropsychological tests and elaboration of appropriate normative data in diagnosing chronic toxic encephalopathy.

ACKNOWLEDGMENTS

This study was supported by grants from the Danish Medical Research Council and Sygekassernes Helsefond.

REFERENCES

Annau Z (1981): The neurobehavioral toxicity of trichloroethylene. Neurobehav Toxicol Teratol 3: 417–424.

Arlien-Søborg P (1991): Organic solvents and the nervous system. Report on a conference sponsored by the Commission of the European Communities and the Danish Ministry of Environment. Luxembourg: The Commission of the European Communities. Directorate-General for Employment, Social Affairs and Education.

Axelson O, Hane M, Hogstedt C (1976): A case referent study on neuropsychiatric disorders among workers exposed to solvents. Scand J Work Environ Health 2:14–20.

Baker EL, White RF, Murawski BJ (1985): Clinical evaluation of neurobehavioral effects of occupational exposure to organic solvents and lead. Int J Ment Health 14:135–158.

Barret L, Faure J, Guillard B, Chornat D, Didier B, Debou J (1984): Trichloroethylene occupational exposure: elements for better prevention. Int Arch Occup Environ Health 53:283–289.

Brackbill RM, Maizlish N, Fishbach T (1990): Risk of neuropsychiatric disability among painters in the United States. Scand J Work Environ Health 16:182–188.

Breslow NE, Day NE (1980): "Statistical Methods in Cancer Research." Lyon: IARC Scientific Publications No. 32.

Christensen AL (1974): "Luria's Neuropsychological Investigation." Copenhagen: Munksgaard.

Christensen JM, Rasmussen K (1990): Exposure of Danish workers to trichloroethylene during the period 1947–1987 (in Danish). Ugeskr Laeger 152:464–467.

Feldman RG, White RF, Currie JN, Travers PH, Lessell S (1985): Long-term follow-up after single toxic exposure to trichloroethylene. Am J Ind Med 8:119–126.

Fidler AT, Baker EL, Letz RE (1987): Neurobehavioral effects of occupational exposure to organic solvents among construction painters. Br J Ind Med 44:292–308.

Grandjean E, Münchinger R, Rurrian V, Haas PA, Knoepfel H-K, Rosenmund H (1955): Investigations into the effects of exposure to trichloroethylene in mechanical engineering. Br J Ind Med 12:131–142.

Gubéran E, Usel M, Raymond L, Tissot R, Sweetnam PM (1989): Disability, mortality, and incidence of cancer among Geneva painters and electricians: A historical prospective study. Br J Ind Med 46:16–23.

Hane M, Axelsson O, Blume J, Hogstedt C, Sundell L, Ydreborg B (1977): Psychological function changes among house painters. Scand J Work Environ Health 3:91–99.

Hänninen H, Eskelinen L, Husman K, Nurminen M (1976): Behavioral effects of long-term exposure to a mixture of organic solvents. Scand J Work Environ Health 2:240–255.

Hartman DE (1988): "Neuro-Psychological Toxicology. Identification and Assessment of Human Neurotoxic Syndromes." New York: Pergamon Press.

Lezak MD (1983): "Neuropsychological Assessment." New York: Oxford University Press.

Lilis R, Stanescu D, Muica N, Roventa A (1969): Chronic effects of trichloroethylene exposure. Med Lavoro 60:595–601.

Lindström K, Riihimäki H, Hänninen H (1984): Occupational solvent exposure and neuropsychiatric disorders. Scand J Work Environ Health 10:321–323.

Maizlish NA, Langolf GD, Whitehead LW, Fine IJ, Albers JW, Goldberg J, Smith P (1985): Behavioral evaluation of workers exposed to mixtures of organic solvents. Br J Ind Med 42:579–590.

Mikkelsen S (1980): A cohort study of disability pension and death among painters with special regard to disabling presenile dementia as an occupational disease. Scand J Soc Med Suppl 16:34–43.

Mikkelsen S, Jørgensen M, Browne E, Gyldensted C (1988): Mixed solvent exposure and organic brain damage. A study of painters. Acta Neurol Scand 78[Suppl 118]:1–143.

Mitchell ABS, Parssons-Smith BG (1969): Trichloroethylene neuropathy. Br Med J 1:422–423.

O'Flynn RR, Monkman SM, Waldron HA (1987): Organic solvents and presenile dementia: a case referent study using death certificates. Br J Ind Med 44:259–262.

Olsen J, Sabroe S (1980): A case-reference study of neuropsychiatric disorders among workers exposed to solvents in the Danish wood and furniture industry. Scand J Soc Med Suppl 16:44–49.

Ørbæk P, Risberg J, Rosén I, Haeger-Aronsen B, Hagstadius S, Hjortsberg V, Regenll G, Rehnström S, Swensson K, Welinder H (1985): Effects of long-term exposure to solvents in the paint industry. A cross-sectional epidemiologic study with clinical and laboratory methods. Scand J Work Environ Health 11[Suppl 2]:1–28.

Plessner W (1915): About trigeminal disease from exposure to trichloroethylene (in German). Neurol Zbl 34:916.

Rasmussen H, Olsen J, Lauritsen J (1985): Risk of encephalopatia among retired solvent-exposed workers. J Occup Med 27:561–566.

Rasmussen K, Sabroe S (1986): Neuropsychological symptoms among metal workers exposed to halogenated hydrocarbons. Scand J Soc Med 14:161–168.

Rasmussen K, Jeppesen HJ, Sabroe S (in press): Psychometric tests in assessment of brain function after solvent exposure. Am J Ind Med.

Ruijten MW, Verberk MM, Sallé HJA (1991): Nerve function in workers with long-term exposure to trichloroethylene. Br J Ind Med 48:87–92.

Smith GF (1970): Investigation of the mental effects of trichloroethylene. Ergonomics 13:580–586.

Spencer PS, Schaumburg HH (1985): Organic solvent neurotoxicity. Facts and research needs. Scand J Work Environ Health Suppl 1:53–60.

Stüber K (1931): Gesundheitsschädigungen bei der gewerblichen Verwendungen des Trichoräthylens und die Möglichkeiten ihrer Verhütung. Arch Gewerbepath Gerwerbehyg 2:398–456.

Trense E (1965): Praktische Ergebnisse der Untersuchung von 546 Triarbeitern. Z Arbeitsmed Arbeitsschutz 15:114–116.

Triebig G (1989): Occupational neurotoxicology of organic solvents and solvent mixtures. Neurotoxicol Teratol 11:575–578.

Triebig G, Schaller K-H, Erzigkeit H, Valentin H (1977): Biochemische Untersuchungen und psycho-

logische Studien an chronisch Trichloräthylen-belasteten Personen unter Berücksichtigung expositionsfreier Intervalle (in German). Int Arch Occup Environ Health 38:149–162.

Triebig G, Trautener P, Weltle D, Saure E, Valentin H (1982): Investigations on neurotoxicity of chemical substances at the workplace (in German). Int Arch Occup Environ Health 51:25–34.

Valciukas JA, Lilis R, Singer RM, Glickman L, Nicholson WJ (1985): Neurobehavioral changes among shipyard painters exposed to solvents. Arch Environ Health 40:47–52.

Wechsler O (1955): "Wechsler Adult Intelligence Scale Manual." New York: New York Psychological Corporation.

American Journal of Industrial Medicine 24:553–565 (1993)

Psychometric Tests for Assessment of Brain Function After Solvent Exposure

Kurt Rasmussen, MD, Hans Jeppe Jeppesen, MSc, and Svend Sabroe, MD

Psychometric testing is a key issue in neuropsychological toxicology assessment. Evaluation of methods for assessing general intellectual impairment is necessary as conventional neurology has been shown to be insensitive to the neurotoxic effects of solvents and metals. This study presents an analysis of a psychometric test battery from an investigation of psycho-organic syndrome in a historical cohort of 96 metal degreasers with long-term exposure to solvents, particularly trichloroethylene.

The neuropsychological test battery was a combination of Wechsler Adult Intelligence Scale (WAIS), Luria, and tests developed in Scandinavia. Linear regression analysis showed a significant dose-response relation between increasing cumulative solvent exposure and impaired psychometric test performance in 9 out of 15 tests. Multivariate analysis, however, suggests that much of the variance was due to confounding variables, especially age, and to a lesser degree, primary intellectual function and word blindness. After control for confounding factors the strongest association with solvent exposure occurred for the following three tests: acoustic-motor function, Paced Auditory Serial Addition Test (PASAT), and the visual gestalt test.

Key words: trichloroethylene, neurotoxicology, solvent exposures, WAIS, neurobehavioral testing

INTRODUCTION

Neurobehavioral testing as a method for evaluating health effects of work place chemicals was introduced about 20 years ago. The neurotoxins of interest have primarily been lead, solvents, and pesticides [Baker et al., 1983]. In occupational epidemiology, neurobehavioral tests may be used as a tool to quantify the functional status of the central nervous system (CNS) or for screening procedures to identify early reversible CNS impairment. There is general agreement regarding the main distinct aspects of CNS function that must be covered by the test battery, i.e., primary intellectual function, learning, memory, and visuospatial and psychomotor function [Baker and Letz, 1986]. On the other hand, problems of standardization and reproducibility remain [Hartman, 1988; Valciukas, 1991]. Questions concerning the diagnostic role seem most urgent. For example: are these tests able to measure mental dysfunction with respect to important competing risk factors such as age, education,

Institute of Epidemiology and Social Medicine, University of Aarhus, Aarhus, Denmark (K.R., S.S.).
Department for Occupational Medicine, University of Aarhus, Aarhus, Denmark (H.J.J.).
Address reprint requests to Kurt Rasmussen, Department of Occupational Medicine, Herning Hospital, DK-7400 Herning, Denmark.
Accepted for publication December 15, 1992.

and primary intellectual function? Which tests should be selected as those with highest predictive value in relation to specific exposures?

The optimal design for examining these issues would be a longitudinal study, giving the possibility of seeing the time course of the test performance in relation to exposure time and confounding variables.

In the present study an assumption to this ideal design has been made in the form of a historical cohort study of metal degreasers mainly exposed to trichloroethylene. The aim was to examine the association between the single psychometric tests and cumulative solvent exposure in order to be able to select the most sensitive test items in neuropsychological assessment of solvent exposed workers.

MATERIALS AND METHODS

Study Population

In the county of Aarhus, Denmark, all metal plants were contacted to obtain information about workers engaged in degreasing and the type of degreasing products used. Of 263 factories contacted, 72 used chlorinated solvents. A questionnaire-based study of neuropsychological symptoms was performed among 240 workers exposed to chlorinated solvents and a control group of 350 unexposed metal workers. From this study population of all identifiable metal degreasers in 1982, all workers who had degreased using either trichloroethylene or fluorocarbon (CFC 113) were selected for clinical examination. Based on these criteria 116 workers were invited to attend a clinical examination for which 99 (85.3%) agreed to participate. The clinical study was undertaken in 1984/1985. The study design is a follow-up study of a historical cohort of metal degreasers from 1982—only this single follow-up examination has been undertaken.

The participants went through a 1-day clinical examination program at a hospital department for occupational medicine. The examination consisted of a medical interview, including an anamnesis covering solvent exposure throughout life, a clinical neurological examination, a neuropsychological examination, and blood and urine laboratory tests. All examinations were performed by the same medical doctor and the same psychologist. Exposure data from the original study were used to create the initial exposure groups in this clinical study. Under the occupational history in the present study, detailed information was requested on types of solvents used for number of hours per week and number of years. When studying brain function, the relevant exposure measurement is a life-long cumulative exposure for all solvents. However, for this study population, the dominant exposure was trichloroethylene for 70 workers and CFC 113 for 25 workers. A cumulative exposure index of all life-long used solvents was made by calculation of number of hours of work with degreasing or other direct solvent exposure per week, multiplied by 45 working weeks per year multiplied by number of years of exposure. From this estimate of total number of exposure hours, three exposure groups were created (Table I) with mean years (and range) of full-time solvent exposure of low exposure: 0.5 (0.05–0.91) years, medium exposure: 2.1 (0.92–3.9), and high exposure 11.0 (4.0–35.6). However, the approach in this study was to examine dose-response relations between an index of continuous exposure and effect variables. There was no external comparison group, but as all degreasers according to the described criteria are included, the range of full-time degreasing is from 1 month to 36 years, which gives the possibility to study

TABLE I. Means of Psychometric Test Scores by Solvent Exposure in a Follow-Up Study of 96 Workers, 1984/1985

	Exposure			Linear regression*		
Psychometric tests[a]	Low (n=19)	Medium (n=36)	High (n=41)	Correlation coefficient	Slope	p value
Vocabulary (h)	58.7	55.2	60.1	0.21	2.0	0.04
Reaction time (m. sec.) (l)	298.8	319.1	322.2	0.21	9.0	0.04
Acoustic motor function (h)						
Repetition 1st group	4.8	3.5	2.3	−0.35	0.7	<0.001
Repetition 3 similar groups	4.2	3.0	1.8	−0.33	1.0	0.001
Discriminatory attention (h)	6.6	5.9	5.8	−0.19	0.4	0.06
Sentence repetition (h)	7.5	6.3	5.7	−0.11	0.3	0.26
PASAT (l)						
Errors	1.8	3.2	3.2	0.17	0.5	0.10
Time (sec.)	53.1	65.1	67.4	0.24	5.0	0.02
Digit span (h)						
Forwards	8.4	7.8	7.8	−0.15	0.2	0.14
Backwards	6.1	5.4	5.2	−0.16	0.2	0.11
Text repetition (h)	23.0	22.0	21.0	−0.19	0.6	0.06
Rey Auditory Verbal Learning Test (h)						
Immediate memory	5.8	5.4	4.9	−0.22	0.3	0.03
Learning	13.1	11.6	11.5	−0.21	0.4	0.04
Retention	11.2	9.8	9.2	−0.15	0.4	0.14
Visual gestalts (l)						
Learning						
Immediate errors	2.9	3.2	5.2	0.33	0.8	0.001
Total errors	3.4	4.1	6.5	0.25	0.9	0.01
Retention						
Immediate errors	3.2	3.6	5.9	0.39	0.1	<0.001
Stone pictures (l)						
Learning	4.6	5.8	6.3	0.1	0.2	0.33
Retention	5.4	7.4	7.8	0.14	0.4	0.17
Digit symbol (h)	47.1	42.9	38.3	−0.23	2.0	0.02
Revised Santa Ana Dexterity (h)						
Right hand	36.7	36.0	32.0	−0.24	1.0	0.02
Left hand	35.1	34.4	27.2	−0.25	2.0	0.01
Both hands	35.0	35.3	26.8	−0.31	3.0	0.002
Luria (l)						
Spread/collect fingers	10.5	27.8	31.7	0.12	0.05	0.23
Fingers vs. 1 finger	0.0	15.8	12.2	0.03	0.02	0.74
Continuous movements	10.5	22.2	36.6	0.03	0.03	0.74
Mira steps (l)						
Stairs, right hand	21.1	30.6	43.9	0.09	0.06	0.37
Stairs, left hand	15.8	41.7	48.8	0.10	0.07	0.32
Angles	26.3	38.9	63.4	0.20	0.13	0.04

*Linear regression analysis: calculation of deviation of mean values from horizontal slope refer to the effect of 10^4 hours of exposure. The linear regression was made on continuous exposure and effect variables.

[a]h: high score indicates good performance; l: low score indicates good performance.

dose-response relations between psychometric test outcome and cumulative solvent exposure over a wide range of exposure.

The symptoms of mental impairment recorded at the medical interview were

tiredness, lack of initiative, reduced learning, impaired memory, impaired attention and psychomotor function, change in mood, anxiety and nervousness, and emotional lability and irritability. The psychological examination consisted of performance in neuropsychological tests and a clinical observation of behavior during the test situation. The psychologist performed his examination blindly with no knowledge of solvent exposure and medical symptoms. The final clinical assessment of the degree of psycho-organic syndrome was based on integrated information about history of symptoms of mental impairment, performance in psychometric tests, and clinical signs of dementia. The psychometric test scores used in the clinical assessment of psycho-organic syndrome were adjusted for the effect of age, primary intellectual function, and word blindness. Psycho-organic syndrome—the clinical outcome variable—is a mild syndrome of dementia, characterized by cognitive impairment, personality changes, and reduced motivation, vigilance, and initiative. Development of a characteristic symptom picture and neuropsychological test results are crucial to the diagnosis.

This article deals with a total of 96 workers, the psychological test for 3 persons being judged as invalid; two exclusions were due to problems with the Danish language by immigrant workers and one exclusion was due to technical problems with the test machinery.

Test Battery

The test battery consisted of subtests from Wechsler Adult Intelligence Scale (WAIS) and Luria in combination with tests developed in Scandinavia in the context of occupational medicine. The following gives a short description of content, scoring, and interpretation of the 15 single tests.

WAIS vocabulary. The original WAIS test comprises 40 words of increasing difficulty where the task is to give an explanation or definition [Wechsler, 1955]. To save time only half of the words were used. The original WAIS version was used. It had been translated from the American version and with American norm values. Score: 2 for correct, 1 for partly correct, 0 for incorrect answers. The scores were summarized and multiplied by 2, the maximum score being 80. Interpretation: primary intellectual level.

Digit symbol. WAIS subtest [Wechsler, 1955]. Corresponding pairs of digits and symbols from 1 to 9 were presented. In each empty box below the digits the symbol should be entered, as many as possible for 90 seconds. Score: the sum of correct entries. Interpretation: visuomotor speed and attention.

Reaction time. Simple reaction time was measured in milliseconds [Söderman et al., 1982; Gamberale, 1985]. Following light signals, a button should be pressed by the subject. The light signals appeared with randomized intervals for periods lasting 2 minutes. This procedure was done in five consecutive trials. Score: mean reaction time in milliseconds for the total time of testing (five by 2 minutes). Interpretation: reaction time, attention, and concentration.

Acoustic-motor function. A test developed from Luria [Christensen, 1974]. High and low frequency tones in eight groups of increasing difficulty (the length of sequences was increased) were given three times each via earphones. After each sequence the tones should be imitated by knocking on the table with a flat hand for low tones and a fist for high tones. Score: 1 point for correct immediate repetition of

the first group and 1 point for correct repetition of all three groups. The maximum score was 8 for the two categories scored separately. Interpretation: acoustic-motor function and immediate memory.

Disciminatory attention. A test developed from Luria [Christensen, 1979]. The subject's attention was disturbed by sound. Ten rows of four to five letters were read aloud by the examiner and interrupted by a "then" before each letter. For each row the letters should be repeated. Score: 1 for correct and 0 for incorrect repetition of each row. Maximum score: 10. Interpretation: attention and immediate memory.

Sentence repetition. A modified version of the Spreen and Benton revised repetition test was used [Bruun and Gade, 1980]; 12 sentences of increasing difficulty were read via earphones and should be repeated after each sentence. Score: 1 for each correct repetition, maximum score being 12. Interpretation: immediate auditory memory.

PASAT. A modified Paced Auditory Serial Addition Test was used where the task was delayed number—repetition [Bruun and Gade, 1980]. Twenty-five single numbers were read aloud while the subject's task was to repeat the forgoing number—maximum 10 seconds were allowed before answering. Score: total time in seconds and number of errors, maximum 25. Interpretation: attention.

Digit span. WAIS subtest. Strings of digits with three to nine digits forward and two to eight digits backwards were read aloud by the examiner. The string length was increased by one digit until errors in two attempts at the same string length. Score: maximum number of digits repeated. Interpretation: immediate memory.

Text repetition. Subtest in Wechsler's memory scale. A short text separated into 18 lines with a maximum of six words in each line should be repeated in extenso after reading. Score: 2 for complete correct line and 1 for incomplete correct line. Maximum score was 36. Interpretation: immediate auditory learning.

Rey's auditory verbal learning test. Fifteen words were read aloud five times and should be repeated after each reading [Lezak, 1983]. After 1 hour, as many words as possible should be repeated without a new presentation. Score: number of correctly repeated words immediately after first and fifth reading and after 1 hour—maximum 15. Interpretation: immediate memory, auditory learning, and retention.

Visual gestalts. Four cards, each with a geometrical figure composed of four structural elements were presented and asked to be redrawn from memory [Andersen, 1976]. Every incorrect or missing part of the figure was counted as an error. The presentation was continued until the figure was drawn correctly. After 1 hour, the subject was asked to reproduce the drawings without new presentation. Score: the sum of errors in the first trial and after 1 hour (maximum 16). Learning errors, maximum 98, is the sum of all errors made until correct reproduction. Interpretation: visuospatial immediate memory, learning, and retention.

Stone pictures. A test developed for this investigation after the same principles as for the other visual memory tests. Black-white slides of 10 stones of different size and shape were shown. The task was to identify the 10 stones among 25 slide-presented stones immediately afterwards. Score: 1 for each correct yes/no, maximum 25. Interpretation: visual learning and retention.

Revised Santa Ana dexterity. Four rows with 12 half-white/half-black circular "pegs" should be rotated 180°, as many as possible for 30 seconds [Hänninen and Lindström, 1979]. Score: correct number of pegs for right, left, and both hands. Interpretation: visuomotor speed and attention.

TABLE II. Multiple Regression Analysis of Psychometric Tests Which Showed Significant Association Between Solvent Exposure and Psychometric Test Score in Linear Regression Analysis (N = 96). For Comparison, Bivariate Results From the Linear Regression Analysis Are Shown*

	Intercept	Solvent exposure		Age		Vocabulary		Arterio-sclerotic disease		Education		Word blindness		Neuro-logical/ psychiatric disease		Present solvent exposure		
Psychometric tests	β	β	p	β	p	β	p	β	p	β	p	β	p	β	p	β	p	R^2
Vocabulary (h)																		
Bivariate	56.3	1.7	0.04															
Multivariate	48.6	0.66	0.42	0.36	<0.001					−6.8	0.01							0.19
Reaction time (l) msec																		
Bivariate	300.2	8.9	0.04															
Multivariate	293.5	5.4	0.19					43.0	0.003					33.4	0.03			0.18
Acoustic-motor function (h)																		
repetition first group																		
Bivariate	4.0	−0.74	0.0006															
Multivariate	4.4	−0.47	0.02	−0.13	<0.001	0.34	0.01	1.67	0.01									0.40
Repetition two similar groups																		
Bivariate	3.4	−0.71	0.001															
Multivariate	7.3	−0.29	0.14	0.11	<0.001													0.34
PASAT (l)																		
Errors																		
Bivariate	2.4	0.49	0.10															
Multivariate	2.0	0.54	0.06									2.3	0.02					0.08
Seconds																		
Bivariate	58.6	5.0	0.02															
Multivariate	36.6	2.6	0.23	0.62	0.004													0.14
Rey A.V.L.T. (h)																		
Immediate memory																		
Bivariate	5.6	−0.28	0.03															
Multivariate	7.2	−0.10	0.43	−0.05	<0.001													0.17
Learning																		
Bivariate	12.3	−0.38	0.04															
Multivariate	10.2	−0.22	0.24	−0.06	0.001	0.36	0.007											0.18
Retention																		
Bivariate	10.2	−0.39	0.14															
Multivariate	7.8	−0.10	0.69	−.011	<0.001	0.51	0.005											0.20

Visual gestalts (l)													
Learning, immediate errors													
Bivariate	3.2	0.77	0.001										
Multivariate	3.0	0.41	0.07	0.11	<0.001	0.31	<0.001						0.30
Learning, total errors													
Bivariate	4.1	0.91	0.01										
Multivariate	6.3	0.40	0.26	0.17	<0.001	−0.7	0.005						0.28
Retention													
Bivariate	3.2	1.3	<0.001										
Multivariate	8.1	1.10	0.001	1.11	<0.001	−0.7	0.001						0.29
Digit symbol (h)													
Bivariate	44.1	−2.3	0.02										
Multivariate	47.2	−0.41	0.64	−0.5	<0.001	1.6	0.02	−6.2	0.04				0.41
Revised Santa Ana dexterity (h)													
Right hand													
Bivariate	35.7	−1.3	0.02										
Multivariate	45.2	−0.06	0.9	0.24	<0.001	−3.3	0.03					2.5 0.02	0.41
Left hand													
Bivariate	33.6	−2.1	0.01										
Multivariate	45.8	−0.75	0.37	−0.34	<0.001								0.22
Both hands													
Bivariate	34.5	−2.8	0.002										
Multivariate	51.0	−1.02	0.24	0.46	<0.001								0.32
Mira (l)													
Stairs, right hand													
Bivariate	1.42	0.06	0.37										
Multivariate	1.08	0.03	0.61			0.46	0.02						0.06
Stairs, left hand													
Bivariate	1.5	0.07	0.31										
Multivariate	1.0	0.03	0.62			0.64	0.002						0.11
Angles													
Bivariate	1.5	0.13	0.04										
Multivariate	1.18	0.11	0.09			0.40	0.04						0.09

*For binary covariates (word blindness, present solvent exposure, alcohol abuse, arteriosclerotic disease) β refers to the effect if the covariate is present. For continuous covariates β refers to the effect of 10^4 hours of exposure, 1 year of age, and 1 score in vocabulary. The parameter estimate β indicates slope-intercept for solvent exposure and significant covariates. p = p value of test for no effect of covariate ($\beta = 0$). R^2 = variance of the test score explained by covariates in the reduced model. h = a high test score indicates good performance. l = a low score indicated a good performance; Rey A.V.L.T. = Rey auditory verbal learning test.

Luria motor function. This involves three elements [Christensen, 1979]. 1) Spreading and collecting fingers for right, left hand, and finally both hands simultaneously. 2) Fingers are alternately opposed to the first finger for right hand, left hand, and finally both hands. 3) Continuous movements with one hand fisted, and the other stretched. Score: a clinical evaluation with values of 1 for unaffected, and 2–4 for light, moderate, and severe affection, respectively. In the final analysis, the outcome is dichotomized with 3 and 4 as affected function. The numbers in Table II are prevalences of affected function. Interpretation: motor coordination.

Mira. A motor function test [Hänninen and Lindström, 1979]. From a few drawn simple figures as "stairs" and "angles," the subject should continue drawing these from one end of the paper to the other, without supporting hand or arm on the table. Score: stairs are scored separately for right and left hand while angles are scored aggregated for both hands on a clinical scale as described under Luria motor function. Interpretation: motor coordination.

Confounding Variables

The following eight variables were considered as potential confounding variables: age, primary intellectual function, word blindness, education, arteriosclerotic disease, neurological psychiatric disease, alcohol, and current solvent exposure. It is well known that test performance in some psychometric tests is affected by age. In the multivariate analysis for control of confounding variables, age was used as a continuous variable. The mean age was 39.6 years, the range being 19–68 years.

The level of intellectual capacity before exposure/before disease plays an important role for present intellectual function. In other studies the WAIS vocabulary test has been found resistant to organic brain damage and is here used as a proxy variable for the primary intellectual function [Lezak, 1983; Mikkelsen et al., 1988]. The age-standardized scale score is used as a continuous variable. The mean score was 12.4 and the range 9–17.

Word blindness may affect performance especially in visual learning and attention tests. There were 14 subjects recorded as word blind on the basis of self-reported previous and present dyslexia.

The level of education may also exert a confounding influence. Two binary variables, school education and skilled education, were tested for the strength of confounding effect in bivariate analyses. School education had the strongest effect and was therefore chosen as the education variable. There were 20 persons with more than 9 years of primary or high school education.

The variable arteriosclerotic disease comprised a positive history or present symptoms or objective signs of systemic arteriosclerosis. This group consisted of 14 persons with intermittent claudication, angina pectoris, acute myocardial infarction, or electrocardiographic signs of coronary arteriosclerosis.

The variable neurological/psychiatric disease involved 11 persons with post-concussional symptoms for more than 3 months, grand mal epilepsy, or primary psychiatric disease of depressive nature.

With regard to alcohol abuse as a confounding variable, the limit was chosen as a weekly consumption of more than 21 drinks or periods as an alcoholic defined as periods with treatment for alcohol abuse. This was the case for five persons.

Current solvent exposure was also considered as a potential confounding variable—53 persons were currently exposed or exposed during the previous month.

Statistical Analysis

The mean test scores used in the statistical analysis are all unadjusted raw scores. Linear regressions are used for continuous variables (Table I). Control of confounding variables was achieved by multiple regression analysis where we have considered covariates as confounders and none as intervening variables. The final model included solvent exposure (irrespective of significance) and confounding variables significant at the 5% level. The statistical analysis was performed with the computer program SPSS/PC.

RESULTS

The mean values of each psychometric test for each of the three groups of increasing solvent exposure are presented in Table I. The direction of good and poor test performance in each test is shown in brackets in Table I. The linear regression analysis expresses the strength of the dose-response relation which was significant in 9 out of 15 psychometric tests.

The multiple regression analysis shows how much of the variance can be explained by solvent exposure and how much by the confounding variables. A considerable part of the test performance could be explained by the age variable in particular. Table II gives the results of multiple regression for those psychometric tests and subtests that were significantly associated to solvent exposure in the linear regression analysis (Table I). The effect of solvent exposure is given for each test as this is the variable of primary interest. Besides that, only confounding variables significant at the 5% level are included in Table II. None of the remaining psychometric tests—those 15 minus 9 tests that were insignificant in linear regression—were significantly associated with exposure after multiple regression.

After controlling for confounding variables, the strongest association with solvent exposure appeared to exist for the following tests: acoustic-motor function, PASAT, and visual gestalts. Significant association at the 5% level was found only for the first repetition of acoustic-motor function and retention of visual gestalts. Age was a significant confounding factor in six of the nine psychometric tests (Table II). Similarly, primary intellectual function (WAIS vocabulary) was a significant confounding factor in three, arteriosclerosis in two, word blindness in two, neurological/psychiatric disease in one, education in one, and present solvent exposure in one of the nine tests. Alcohol abuse was an insignificant confounder in the analysis as in Table II. Some tests are shown to be age resistant in the multivariate analysis, this being the case for discriminatory attention, sentence repetition, digit span, and the stone picture recognition test. However, these tests were not found to be sensitive to solvent exposure and are therefore not included in Table II. Besides the results of the multivariate analyses, Table II also gives a list of those psychometric tests found to be sensitive to neuropsychological impairment after solvent exposure in the present investigation.

Figure 1 is a visualization of the predicted value from the multiple regression analysis of solvent exposure and the visual gestalt retention test, controlled for the effect of age which was the strongest confounding variable for this test. In Figure 1 regression lines are shown for two different age groups. Exposure to solvents over a period of 60,000 hours, corresponding to 33 years of full-time exposure, resulted in

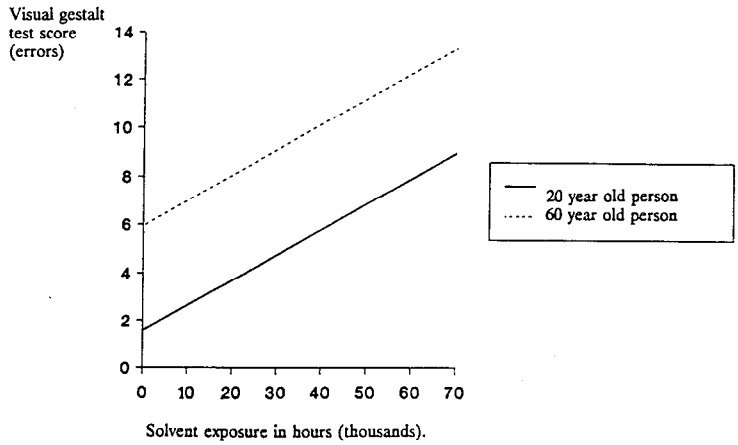


Fig. 1. Illustration of the predicted values from selected steps in multiple regression model of test performance in the visual gestalt retention test in relation to solvent exposure and age.

a significant increase of errors in the visual gestalt retention test, the deterioration in performance being equivalent to an age difference of 40 years.

Figure 2 is a corresponding model presentation of the results of the predicted value from multiple regression analysis of solvent exposure and the WAIS digit symbol test, with age and education in the model. The figure presents regression lines calculated for three groups differing with regard to age and education. There seems to be an association between solvent exposure and test result, though this association was barely significant and was substantially weaker than the one related to age and education.

DISCUSSION

There are several human studies from the late 1960s reporting adverse effects on performance in behavioral tests after acute experimental exposure to e.g., the solvent trichloroethylene [Stopps and McLaughlin, 1967; Vernon and Ferguson, 1969]. Single psychometric tests have also been used to monitor the effects of work place exposure, including the effect of regulatory controls [Olson et al., 1981]. However, Hänninen [1971] gave neuropsychological testing in occupational studies a breakthrough by her pioneering work on carbon disulfide. Since then a variety of studies [Hänninen et al., 1976; Fidler et al., 1987; Mikkelsen et al., 1988; Bleecker et al., 1991; Rasmussen et al., 1993] have used these testing instruments, which have been evaluated in several reviews [Anger, 1985; Baker and Letz, 1986; Gamberale, 1985; White and Feldman, 1987; White and Proctor, 1992]. Hartman's [1988] monograph presents a broad updated review with guidelines for neuropsychological toxicology.

Nowadays, psychometric tests play a key role in the armamentarium for assessing toxic effects of solvents on the CNS. It is widely accepted that neuropsycho-

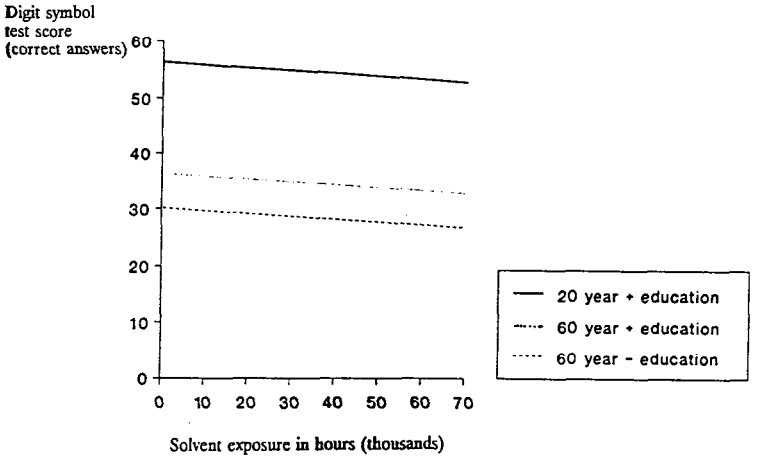


Fig. 2. Illustration of the predicted values from selected steps in multiple regression model of test performance in the WAIS digit symbol test in relation to solvent exposure, age, and education.

logical methods are more sensitive for detecting early behavioral dysfunction resulting from industrial neurotoxic exposures than conventional neurological examination. However, some issues of neuropsychological testing have not yet been satisfactorily resolved, the most important being relevant test selection, the role of confounding factors, and the biological significance of specific levels of impairment in test performance.

The test battery in the present study is built on modified WAIS and Luria tests, supplemented with tests from Scandinavian batteries of occupational neuropsychological tests. In Denmark, there does not exist a uniform test battery, as for example, in Sweden. The present study indicates nine tests as the most sensitive to effects of solvent exposure as demonstrated by a dose-response relationship. The applied test battery consisted of 15 tests, and at the chosen level of significance of 5%, an association between a psychological test and solvent exposure could be expected just because of stochastic variation. However, for nine of the tests employed, the probabilities associated with observed effects were much lower than 0.05. Such a joint result is highly unlikely to occur by chance alone.

Confounding variables seem to have had a very strong influence, substantially reducing the association to solvent exposure. The predominant confounding variable was age. Some psychometric tests are known from standardization studies to be related to age and, to a lesser degree, education [Andersen, 1976]. However, a set of age-standardized data exists only for the WAIS tests [Wechsler, 1955]. The outcomes employed in this study were unadjusted raw scores, so it was expected that age would have an important confounding influence. The role of the predominant confounder age has been ruled out by analysis of interaction. No interaction was found between age and solvent exposure in relation to psycho-organic syndrome, the effect so being conceptually independent.

The exposure variable "number of years of solvent exposure" is by nature related to age. In the present study population, this relationship is very close, i.e., almost none of the elderly had a low exposure. In this situation, control of the confounding variable tends to overestimate the effect of age and to underestimate the effect of solvent exposure. The strong effect of age as a confounder should be interpreted with respect to this.

Other relevant, but in this study relatively weak, confounding variables were primary intellectual level, word blindness, and education. It is a potential problem to distinguish between acute and chronic effects of solvent exposure. In this study group, only 53 persons were exposed during the last month. In the analysis recent solvent exposure was found to be insignificant as a confounding variable.

The major methodological drawback of the present study is the uncertain estimate of individual prior intellectual function based on the WAIS vocabulary test. This gives an uncertain estimate of whether the present level is acquired or related to primary function. Furthermore, the low R^2 values show that the chosen exposure and confounder variables explain only little of the variance in test performance. This leaves a possibility for residual confounding of unknown nature. Of other types of potential bias, selection bias should be mentioned, though this should be limited through the design of a historical cohort study.

In accordance with other investigations [Anger, 1985], the present study has found psychometric tests sensitive for the purpose of measuring neuropsychological effects of solvent exposure. Study design, analytical approach, and main findings correspond to a recent study with dose-related neurobehavioral effects among workers from two paint manufacturing plants [Bleecker et al., 1991]. Furthermore, the present results point to tests of attention, and also to visuospatial function, as particularly sensitive tests. It must be stressed, however, that test performance is only one part of the final assessment of neuropsychological function when the diagnosis of toxic encephalopathy is to be established. Lezak [1984] has addressed the issues of emotional deficits and executive capacities, for which no standardized assessment techniques are available, but where elaborate questioning and clinical evaluation are of importance.

The latest international conference of solvents and neurotoxicity has found fields of neuropsychology of great importance for further research [Arlien-Søborg, 1991]. Recommended aspects include studies of standardization of neuropsychological tests with identification of sensitive tests and test batteries, together with elaboration of tests or combination of tests, and test batteries measuring primary intellectual function.

ACKNOWLEDGMENTS

This study was supported by grants from the Danish Medical Research Council and Sygekassernes Helsefond.

REFERENCES

Andersen R (1976): Verbal and visuo-spatial memory. Scand J Psychol 17:198–204.

Anger WK (1985): Neurobehavioral tests used in NIOSH-supported worksite studies 1973–1983. Neurotoxicol Teratol 7:359–368.

Arlien-Søborg P (1991): Organic solvents and the nervous system. Report on a conference sponsored by the Commission of the European Communities and the Danish Ministry of Environment. Luxembourg: The Commission of the European Communities. Directorate-General for Employment, Social Affairs and Education.

Baker EL, Feldman RG, White RF, Harley JP, Dinse GE, Berkey CS (1983): Monitoring neurotoxins in industry: Development of a neurobehavioral test battery. J Occup Med 25:125–130.

Baker EL, Letz R (1986): Neurobehavioral testing in monitoring hazardous workplace exposures. J Occup Med 28:987–990.

Bleecker ML, Bolla KI, Agnew J, Schwartz BS, Ford P (1991): Dose-related subclinical neurobehavioral effects of chronic exposure to low levels of organic solvents. Am J Ind Med 19:715–728.

Bruun P, Gade S (1980): "Extended Manual of Neuropsychological Testing" (in Danish). Copenhagen: National Hospital.

Christensen AL (1979): "Luria's Neuropsychological Investigation." Copenhagen: Munksgaard.

Fidler A, Baker EL, Letz RE (1987): Neurobehavioral effects of occupational exposure to organic solvents among construction painters. Br J Ind Med 44:292–308.

Gamberale F (1985): Use of behavioral performance tests in the assessment of solvent toxicity. Scand J Work Environ Health 11, suppl 1:65–74.

Hänninen H (1971): Psychological picture of manifest and latent carbon disulfide poisoning. Br J Ind Med 28:374–381.

Hänninen H, Eskelinen L, Husman K, Nurminen M (1976): Behavioral evaluation of workers exposed to mixtures of organic solvents. Scand J Work Environ Health 2:240–255.

Hänninen H, Lindström K (1979): "Behavioral Test Battery for Toxicopsychological Studies." Helsinki: Institute of Occupational Health.

Hartman DE (1988): "Neuropsychological Toxicology. Identification and Assessment of Human Neurotoxic Syndromes." New York: Pergamon Press.

Lezak MD (1983): "Neuropsychological Assessment." New York: Oxford University Press.

Lezak MD (1984): Neuropsychological assessment in behavioral toxicology—developing techniques and interpretation issues. Scand Work Environ Health 10, suppl. 1:25–29.

Mikkelsen S, Jørgensen M, Browne E, Gyldensted C (1988): Mixed solvent exposure and organic brain damage. A study of painters. Acta Neurol Scand 78, suppl. 118:1–143.

Olson BA, Gamberale F, Grönqvist B (1981): Reaction time changes among steel workers exposed to solvent vapors. Int Arch Occup Environ Health 48:211–218.

Rasmussen K, Jeppesen HJ, Sabroe S (1993): Solvent induced chronic toxic encephalopathy. Am J Ind Med 23:779–792.

Söderman E, Kjellberg A, Olson BA, Iregren A (1982): "Standardization of Simple Reaction Time for Behavioral Toxicological Studies" (in Swedish). Stockholm: National Institute of Occupational Health.

Stopps GJ, McLaughlin M (1967): Psychophysiological testing of human subjects exposed to solvent vapors. Am Ind Hyg Assoc J 5:43–50.

Valciukas JA (1991): "Foundations of Environmental and Occupational Neurotoxicology." New York: Van Nostran Reinhold.

Vernon RJ, Ferguson RK (1969): Effects of trichlorothylene on visual-motor performance. Arch Environ Health 18:894–900.

Wechsler D (1955): "Wechsler Adult Intelligence Scale. Manual." New York: New York Psychological Corporation.

White RF, Feldman RG (1987): Neuropsychological assessment of toxic encephalopathy. Am J Ind Med 11:395–398.

White RF, Proctor SP (1992): Research and clinical criteria for development of neurobehavioral test batteries. J Occup Med 34:140–148.

Acta Neurol Scand 1993: 87: 200–204
Printed in Belgium – all rights reserved

ACTA NEUROLOGICA SCANDINAVICA
ISSN 0001-6314

Clinical neurological findings among metal degreasers exposed to chlorinated solvents

Rasmussen K, Arlien-Søborg P, Sabroe S. Clinical neurological findings among metal degreasers exposed to chlorinated solvents.
Acta Neurol Scand 1993: 87: 200–204. © Munksgaard 1993.

Among industrial solvents in present use trichloroethylene belongs to those which have been the concern of most neurological and occupational investigations since the beginning of this century. Reports on a broad spectrum of neurotoxicity are however mostly based on case-studies and accidental circumstances. The object of this study was to examine clinical neurological manifestations after long-term exposure to degreasing solvents, mainly trichloroethylene. The population was 99 metal degreasers, the design a historical cohort study. The most marked finding was a highly significant dose-response relation between solvent exposure and motor dyscoordination – a finding that was retained after multivariate control of relevant confounders. Vibration thresholds increased by solvent exposure at bivariate level, but the multivariate analysis showed that age was explaining most of the increase. No significant cranial nerve dysfunction was found.

K. Rasmussen [1], P. Arlien-Søborg [2], S. Sabroe [1]

[1] Institute of Epidemiology and Social Medicine, University of Aarhus, [2] Department of Neurology, Hvidovre Hospital, Copenhagen, Denmark

Key words: solvents; trichloroethylene; cranial neuropathy; motor dyscoordination; vibration threshold

Kurt Rasmussen, Department of Occupational Medicine, Herning Hospital, DK-7400 Herning, Denmark

Accepted for publication June 30, 1992

Soon after the introduction of trichloroethylene as a degreasing agent in the metal industry in the beginning of this century, there were reports of neurological manifestations related to exposure (1). Since then there have been current case histories on cranial nerve disturbance or fatal cases with severe histological alterations in the central nervous system – most reports are after accidental overexposure inside tanks (2, 3). But cranial neuropathy after short term exposure to trichloroethylene under normal and common conditions of exposure has also been reported (4).

Current evidence of solvent-related neurotoxicity exists as a histologically verified symmetrical sensorymotor peripheral neuropathy, which has been demonstrated following exposure of human and animals to a few specific solvents, primarily n-hexane and carbondisulfide and to some degree trichloroethylene. More debatable is the evidence linking solvent exposure to other neurological syndromes such as cerebellar ataxia, Parkinsonism and the psychoorganic syndrome or chronic toxic encephalopathy.

In a recent thesis based on a clinical epidemiological study of painters and a control group of brick-layers there were found significantly increased relative risks of dementia and of general motor dyscoordination (5). The risk of dyscoordination was 2.4 for painters with a medium and 5.5 for painters with a high solvent exposure level.

The neurotoxicity of trichloroethylene is characterized by cranial neuropathy. Trigeminal sensory neuropathy is dominating but also dysfunction of cranial nerves I, VII, X and XII, occurs (2, 3, 6). A number of clinical epidemiologic studies through the last decade have indicated that encephalopathy may develop as well (7–9).

This study population of metal workers has mainly been exposed to trichloroethylene. The purpose of the study was to examine the association between long-term occupational exposure to degreasing solvents and the outcome of a clinical neurological examination with focus on motor dyscoordination, affection of vibration thresholds and cranial nerve disturbances.

Material and methods

The study population was all identifiable workers engaged in metal degreasing in the county of Aarhus, Denmark. Of 263 factories contacted 77 used chlorinated solvents. A questionnaire-based study of neuropsychological symptoms was performed among 240 workers exposed to chlorinated solvents and a control group of 350 unexposed metal workers. From this study population of all identifiable metal degreasers in 1982, all workers who had degreased using either the classical chlorinated solvent trichloroethylene or the new substituting fluorocarbon (CFC 113), were selected for a clinical examination. Based on these criteria 116 workers were invited to attend a clinical examination for which 99 agreed to participate – the rate of participation was

85.3%. The clinical study was undertaken in 1984/85. The study design is a follow-up study in a historical cohort of metal degreasers from 1982, only this single follow-up examination has been undertaken.

The participants went through a one-day clinical examination program all performed by the same medical doctor and the same psychologist at a hospital department for occupational medicine. The examination consisted of a medical interview, a clinical neurological examination, a neuropsychological examination and blood and urine laboratory tests. As well as the medical anamnesis a detailed life-long occupational history was taken, with information of types of solvents used in number of hours per week, and number of years, together with general hygienic working conditions. Cumulative exposure to solvents was categorized in 3 groups where the mean full time exposure was low: 0.5 year, medium: 2.1 years, and high: 11.0 years. The dominant exposure for 70 workers was trichloroethylene with a mean exposure time of 7.1 years, 35.0 h per week and for 25 persons CFC 113 with a mean exposure time of 4.2 years and 15.1 h per week.

Present or recent exposure to trichloroethylene was quantified by blood and urine analysis of the metabolites trichloroacetic acid (TCA) and trichloroethanol (TCE). The mean urine TCA in the most highly exposed group was 7.7 mg/l with a maximum TCA of 26.1 mg/l. However, historical exposure data reviewing all measurements of trichloroacetic acid in urine, notified to the Danish Labour Inspection Service during the period 1947–87, indicates a fairly constant and high exposure level corresponding to about 40–60 mg/l urine TCA from the mid 50s to the mid 70s which is a time period relevant to this study population (10).

The neurological examination consisted of a qualitative, clinical examination of cranial nerve function, coordination, reflexes, sensibility and muscle strength supplemented by a quantitative measurement of vibration threshold by a biothesiometer. The function of the olfactory nerve was tested on each side separately by successive blind presentation of small brown glasses with ground coffee, lavender solution and petrol. An abnormal results was recorded when the subject was not able to smell both of the first two substances. For testing the sensitive function of the facial nerve, which subserves taste of the anterior 2/3 of the tongue, we used four test solutions: saccharine 40%, NaCl 10%, citric acid-monohydrate 10%, and kininchloride 0,5%. Each test was done separately at both the right and left side of the tongue – 3 or 4 incorrect answers each after two attempts were scored as abnormal. The coordination tests assessed resting or static tremor, finger-nose, heel-knee coordination, diadochocinesis, Romberg test and gait (normal gait with open and closed eyes followed by line-walking at a distance of 3 meter). Each test was scored after clinical assessment as normal or in the presence of dyscoordination as abnormal. Vibration threshold was measured by a biothesiometer (Lübche Vario R 51-220 L, H.K. Lübche Biomedical Instruments). A handheld mains operated unit with a plastic tactor vibrated at 50 Hz. The applied voltage needed to register a sensation of vibration was recorded at a linear scale from 0–220 V, where the voltage is proportional to the square root of the amplitude of vibration. Subjects were measured at the second fingerpulp, the distal styloid of the radius bone, the medial maleolus, and the first toe pulp, all bilaterally. The mean of 2 measurements of each location, was registered.

Studying neurological outcome four variables were considered as potential competing risk factors: age, neurological disease, arteriosclerotic disease, and alcohol abuse. Age is in the multivariate analysis for confounding control used as a continuous variable. The mean age was 39.6 years, the range was 19 to 68 years. The variable neurological/psychiatric disease comprised 11 persons with postconcussional symptoms for more than 3 months, epilepsy (generalized tonic clinic seizures) and primary psychiatric disease of depressive nature. The variable arteriosclerotic disease was composed of a positive history of present symptoms or objective signs of systemic arteriosclerosis – this group consisted of 14 persons. The limit for alcohol abuse as a confounder was chosen as a weekly consumption of more than 21 drinks or periods as an alcoholic defined as periods with treatment for alcohol abuse. This was the case for 5 persons. Statistical analysis was based on χ^2 test for trend (11), linear and multiple regression analysis.

Results

Table 1 gives the number of metal workers with affected cranial nerve function at an objective neurological examination. A trend to dose-response relation is shown, although the numbers with positive neurological outcome are small.

At the evaluation for dyscoordination static tremor was found in four cases, finger-nose dyscoordination in 13, heel-knee dyscoordination in 16, dysdiadochocinesis in 1, affected gait in 17 and a positive Romberg test in 10 cases. It is assumed that a relation between solvent exposure and dyscoordination applies do dyscoordination in general and not to any specific type of dyscoordination. The combined performance as measured by the number of abnormal tests is expected to measure an underlying common factor as a cause of dyscoordination. Therefore a

Table 1. Cranial nerve dysfunction by solvent exposure. Number and (%) of metal workers with abnormal function at clinical examination

Cranial nerves	Solvent exposure level: Low (n=21)	Medium (n=37)	High (n=41)	p-value
I Olfactory nerve, sense of smell	0 (0.0)	0 (0.0)	4 (9.8)	0.03*
V Trigeminal nerve, sensory function	1 (4.8)	2 (5.4)	4 (9.8)	0.42**
VII Facial nerve, taste	3 (14.3)	6 (16.2)	9 (22.0)	0.42**

* Fisher's exact test.
** Mantel-Haenzel test for linear association.
Exposure groups:
Cumulative full-time solvent exposure, mean and range:
- low: 0.52 (0.05–0.90) years
- medium: 2.2 (0.91–3.8) years
- high: 11.0 (4.0–35.6) years.

sum variable of the 6 coordination tests were created. Table 2 shows that 66 of the 99 examined persons had no motor dyscoordination, 16 failed in 1 test, 11 in 2 tests, 1 in 3 tests, and 5 in 4 or more tests. A significant trend of dyscoordination from low to high solvent exposure is demonstrated. This is further illustrated in Fig. 1 where the mean numbers of dyscoordination outcome is presented for 3 exposure groups.

Vibration threshold was recorded at 4 locations bilaterally. Linear regression showed significant relation to solvent exposure at 7 of 8 points when they were analysed individually – p-values were less than 0.02 except at the left wrist ($p = 0.24$). To get one single expression of vibration threshold the frequencies of the 8 thresholds were pooled for analysis to get a summary threshold perception which was highly significantly associated to solvent exposure (Fig. 2).

The bivariate associations are tested multivariately in Table 3. For motor dyscoordination the association to solvent exposure was able to hold, none

Table 2. Distribution of number and (%) of abnormal coordination tests according to solvent exposure level

Number of abnormal coordination tests	Solvent exposure level: Low (n=21)	Medium (n=37)	High (n=41)
None	19 (90.5)	27 (73.0)	20 (48.8)
1	1 (4.8)	6 (16.2)	9 (22.0)
2	1 (4.8)	3 (8.1)	7 (17.1)
3	0 (0.0)	0 (0.0)	1 (2.5)
4–6	0 (0.0)	1 (2.7)	4 (9.8)

X^2-trend analysis: Low versus medium ~ p-value=0.16.
Low versus high ~ p-value=0.003.

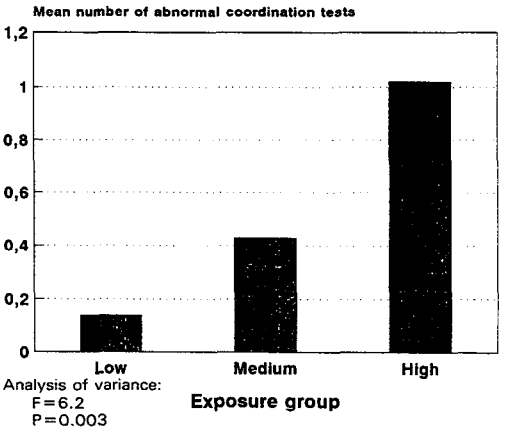


Fig. 1. Trend of motor dyscoordination by solvent exposure.

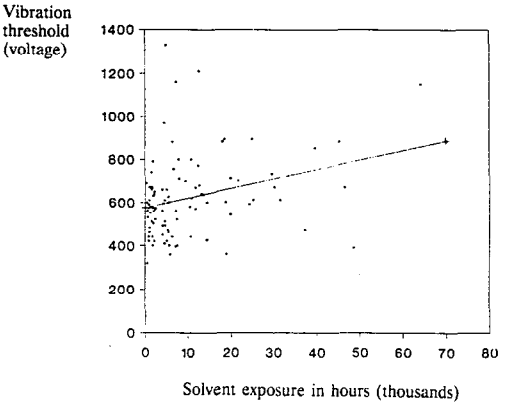


Fig. 2. Regression analysis of bivariate association between solvent exposure and vibration threshold summarized for 8 body locations. Linear regression: p-value = 0.004.

of 4 confounders had any considerable effect. The opposite was seen in the vibration threshold test. After confounding control the association between increased vibration threshold and solvent exposure vanished. The dominating covariate was age and to a lesser degree arteriosclerotic disease. To show the separate effect of the significant confounder age on vibration threshold, but also the importance of the other potential confounders, two steps of multiple regression is shown in Table 3.

Discussion

The main finding in this study was a dose-response relation between solvent exposure and clinical neurological signs of dyscoordination. Less clear was a

Table 3. The association between solvent exposure and summarized variables of motor dyscoordination and vibration threshold after multiple regression controlling for the effect of confounders: age, neurological disease, arteriosclerotic disease and alcohol abuse.
For comparison bivariate results (linear regression analysis). The parameter-estimate β indicate slope/intercept for solvent exposure and covariates.
P=p-value of test of no effect of covariate (β=0).

	Dyscoordination				Vibration threshold					
	Bivariate		Multivariate		Bivariate		Multivariate			
							Model I		Model II	
	β	P	β	P	β	P	β	P	β	P
Intercept	0.39		0.43		576.2		267.4		290.8	
Solvent exposure	22.6	0.01	24.5	0.01	44.0	0.004	10.1	0.45	5.0	
Age			−2.7	0.98			8.6	<0.0001	8.0	
Neurological disease			−0.07	0.84					−23.0	
Arteriosclerotic disease			−0.23	0.49					84.3	
Alcohol abuse			−0.20	0.68					−32.7	

For binary covariates (neurological and arteriosclerotic disease, alcohol abuse) β refers to the effect if the covariate is present. For continuous covariates β refers to the effect of 10^4 hours of exposure and one year of age.

trend of cranial nerve disturbance. Only the function of the olfactory nerve was significantly affected, while this was not the case for the trigeminal nerve, as could be expected according to the literature (1, 4, 19). Also increased vibration threshold was found associated to solvent exposure. However, this finding was not able to withstand a multivariate analysis where age showed to be a strong confounder, as age and exposure was strongly correlated. It must be stressed that the etiological linkage between solvent exposure and neurological outcome, in the present study is based on dose-response relationships as no external control group was included.

Some comments on the shortcomings of this study. The short follow-up period of 2 1/2 years for this historical cohort gives possibility to secondary healthy worker selection. However, such a selection bias tends to underestimate the proven relationship between solvents and neurological effects. Some plausible explanations might lie behind the observed influence of potential confounders. The recorded alcohol habits had no significant relation to dyscoordination or increased vibration threshold. The reason may be difficulty in getting true and precise information on the amount of alcohol consumption based on anamnestic information from the examined person. Age is a somewhat problematic confounder in this study. Age is by nature strongly correlated to cumulative exposure – the age distribution of this material was from 19 to 68 years. None of the young workers had any possibility of being categorized as highly exposed, so genuine age adjustment can only be done by the relatively few old workers with low cumulative exposure. This makes age such a strong confounder in this model of analysis.

The result of dyscoordination is in good accordance with findings in a recent Danish investigation of solvent exposed housepainters and non-exposed bricklayers, in a design much like the one in this study (5). Besides that clinical neurological signs of dyscoordination have been studied only in a Swedish epidemiological studies, with no equivocal results (12–14). The CNS structures most likely involved in dyscoordination as assessed in this study are cerebellum, the brain stem and the basal ganglias. The pattern of the proven dyscoordination indicates that cerebellar and vestibular structures are predominantly impaired. Vestibular dysfunction following acute as well as chronic solvent intoxication has been indicated by a number of studies (15, 16).

Increase of vibration threshold measured by a biothesiometer has been suggested as a sensitive indicator of peripheral neuropathy, although the clinical significance is not clarified (17). In a Swedish study from 1980 an exposed group of car and industrial spray painters had higher vibration threshold than two control groups of non-exposed workers (10, 12). The finding was similar in all age strata – however, a full confounding control was not performed. A recent American study has suggested significantly higher thresholds of vibration sense perception in solvent exposed painters as compared with non-exposed boiler makers (18). A limitation also of this study is insufficient confounding control.

Discrete signs of trigeminal neuropathy after long-term exposure to trichloroethylene has been demonstrated in a couple of newer studies. A French study with 188 workers, 1/3 degreasers, found signs and symptoms of trigeminal impairment in 22% of the high-exposed group compared to 7% in low-exposed group – the exposure characteristics in this study are badly illucidated (7). Later the same research group has studied a selected group of 104 subjects highly exposed to trichloroethylene by clinical examination

and by trigeminal somato-sensory evoked potentials (19). Disturbed trigeminal somato-sensory evoked potentials were found in 40 subjects which was predictable from their clinical symptoms. A Dutch study of 31 printing workers exposed for about 20 years at levels around the hygienic limit value revealed a prolonged refractory period of the trigeminal nerve compared to the control group (8).

Despite intense scientific activity throughout the last decades many questions still seem unsolved regarding the nature and extent of neurotoxicity of solvents. A clear distinction between clinical and subclinical neuropathy has not been made in all studies, rendering interpretation difficult. In most studies of solvent exposed groups the rates of peripheral nervous system toxicity have apart from hexacarbons been lower than the central nervous system effects. Another part of this study has dealt with neuropsychological assessment of cognitive dysfunction. The risk of developing a psycho-organic syndrome was proportional to the exposure level but only significant among the most highly exposed with a mean exposure of 11 years of full-time exposure (9).

The present findings suggest general dyscoordination and cranial nerve disturbances after long-term, occupational but non-accidental circumstances of exposure to trichloroethylene. However, more studies are needed to understand the potential toxicity of this compound. The latest international conference on solvents and neurotoxicity in Copenhagen in 1990 has stated the needs for future research (20). Basic research on the mechanisms of solvent toxicity and epidemiological research in the design of historical cohort studies with proper confounder control were particularly recommended. This should also include further evaluation of the sensitivity and predictive value of clinical methods.

Acknowledgements

This study was supported by grants from the Danish Medical Research Council and Sygekassernes Helsefond.

References

1. PLESSNER W. About trigeminal disease from exposure to trichloroethylene (in German). Neurol Zbl 1915: 34: 916.
2. LAWRENCE WH, PARTYKA EK. Chronic dyshagia and trigeminal anaesthesia after trichloroethylene exposure. An Int Med 1981: 95: 710.
3. FELDMAN RG, WHITE RF, CURRIE JN, TRAVERS PH, LESSELL. Long-term follow-up after single toxic exposure to trichloroethylene. Am J Ind Med 1985: 8: 119–126.
4. MITCHELL ABS, PARSSONS SMITH BG. Trichloroethylene neuropathy. Br Med J 1969: 1: 422–423.
5. MIKKELSEN S, JØRGENSEN M, BRONNE E, GYLDENSTED C. Mixed solvent exposure and organic brain-damage. Acta Neurol Scand 1988: 78 (suppl. 118): 1–143.
6. SPENCER PS, SCHAUMBURG HH. Organic solvent neurotoxicity. Scand J Work Environ Health 1985: 11 (suppl. 1): 53–60.
7. BARRET L, FAURE J, GUILLARD B, CHOMAT D, DIDIER B, DEBRU JL. Trichloroethylene occupational exposure: elements for better prevention. Int Arch Occup Environ Health 1984: 53: 283–289.
8. RUIJTEN MWMM, VERBERK MM, SALLÉ HJA. Nerve function in workers with long-term exposure to trichloroethylene. Br J Ind Med 1991: 48: 87–92.
9. RASMUSSEN K, JEPPESEN HJ, SABROE S. Solvent induced chronic toxic encephalopathy. Am J Ind Med (in press).
10. CHRISTENSEN JM, RASMUSSEN K. The exposure of Danish workers to trichloroethylene 1947–88 (in Danish). Ugeskr Læger 1990: 152: 464–467.
11. ARMITAGE P. Test for linear trends in proportions and frequencies. Biometrics 1955: 11: 375–386.
12. ELOFSSON S-A, GAMBRALE F, HINDMARSH T et al. Exposure to organic solvents: a cross-sectional epidemiologic investigation on occupationally exposed car and industrial spray painters with special reference to the nervous system. Scand J Work Environ Health 1980: 6: 239–273.
13. HUSMAN K, KARLI R. Clinical neurological findings among carpainters exposed to a mixture of organic solvents. Scand J Work Environ Health 1980: 6: 33–39.
14. ØRBÆK P, RISBERG J, ROSÉN I et al. Effect of long-term exposure to solvents in the paint industry. Scand J Work Environ Health 1985: 11 (suppl. 2): 1–28.
15. ARLIEN-SØBORG P, ZILSTORFF K, GRANDJEAN B, PEDERSEN LM. Vestibular dysfunction in occupational chronic solvent intoxication. Clin Otolaryngol 1981: 6: 285–290.
16. ÖDKVIST L, LARSBY B, THAM R, HYDÉN D. Vestibulo-oculomotor disturbances caused by industrial solvents. Otolaryngol Head Neck Surg 1983: 91: 537–539.
17. BLOOM S, TILL S, SØNKSEN P, SMITH S. Use of biothesiometer to measure individual vibration thresholds and their variation in 519 non-diabetic subjects. Br Med J 1984: 288: 793–795.
18. DEMERS RY, MARKELL BL, WAKEBE R. Peripheral vibratory sense deficits in solvent exposed painters. J Occup Med 1991: 33: 1051–1054.
19. BARRET L, GARREL S, DANEL V, DEBRU JL. Chronic trichloroethylene intoxication: a new approach by trigeminal-evoked potentials? Arch Environ Health 1987: 42: 297–302.
20. Organic solvents and the nervous system. Report on a conference sponsored by the Commission of the European Communities and the Danish Ministry of the Environment. Danish Environmental Protection Agency, Strandgade, 1401 Copenhagen K, DK. Copenhagen, 1990.

Int Arch Occup Environ Health (1993) 64:445–448

International Archives of
Occupational and
Environmental
Health

Subclinical affection of liver and kidney function and solvent exposure

Kurt Rasmussen[1], **Carl-Henrik Brogren**[2], **and Svend Sabroe**[1]

[1]Institute of Epidemiology and Social Medicine, University of Aarhus, DK-8000 Århus C, Denmark
[2]Danish National Institute of Occupational Health, DK-2100 Copenhagen, Denmark

Received May 18 / Accepted September 19, 1992

Summary. The role of solvents as hepato- and nephrotoxic agents under present-day exposure levels is still unclear. The purpose of this study involving 99 metal degreasers was to examine dose-response relationships between long-term exposure of mainly trichloroethylene and a battery of liver function tests and one nephrotubular enzyme test. Serum γ-glutamyltransferase and urinary *N*-acetyl-β-glucosaminidase were elevated by increasing solvent exposure at bivariate level. The significance of this relationship, however, was not able to withstand a multiple regression analysis, with age and alcohol abuse as confounding variables. The conclusion is that of a nonsignificant association between solvent exposure and tests screening for early liver and kidney dysfunction.

Key words: Hepatotoxicity – Nephrotoxicity – Organic solvents – Trichloroethylene

Introduction

Some solvents from the group of halogenated hydrocarbons are known to be potent hepatotoxic and nephrotoxic chemicals [11]. This is especially the case for carbon tetrachloride. Of greater interest for present-day exposure is the question of whether currently used halogenated solvents, for example, trichloroethylene, are able to affect liver and kidney function, primarily on a subclinical level. An early liver toxic effect can be detected on the basis of several blood-borne markers, these being parenchymatous, bile secretory, and liver synthetic parameters. Previously, nephrotoxicity was more difficult to measure at low-effect levels. However, studies over the past decade have revealed urinary *N*-acetyl-β-glucosaminidase (NAG) activity as one of the most valuable and sensitive indicators of renal injury in diabetes, kidney diseases, and exposure to various nephrotoxins such as metals and solvents [7, 8]. NAG is a lysosomal enzyme present in the renal tubular cells and excreted into urine after nephrotoxic exposure. NAG activity is increased in the urine even at subclinical stages of nephropathy and may be used in screening for necrosis of kidney tubular cells.

The purpose of this investigation was to examine dose-response relationships between exposure to degreasing solvents, mainly trichloroethylene, and liver and kidney functions as detected on the basis of urinary and blood-borne markers.

Correspondence to: K. Rasmussen

Material and methods

The study population comprised 240 workers engaged in metal degreasing with chlorinated solvents at 72 different factories in the county of Aarhus, Denmark. The design was a cross-sectional study. From the overall population those were selected who had degreased with trichloroethylene or fluorocarbon (CFC 113). A total of 116 workers fulfilled the criteria and were invited to attend a clinical examination, and of these, 99 agreed to participate (85.3%). The age range of participants was 19–68 years, mean 39.4 years. There was no external control group. All degreasers, according to the criteria described, were included, independent of the duration of exposure. The range of full-time degreasing was 1 month–36 years, which means that internal groups for comparison could be established, suitable for dose-response analyses.

The participants went through a 1-day clinical examination program at a hospital department for occupational medicine. The examination consisted of a medical interview, a clinical neurological examination, a neuropsychological examination, and blood and urine laboratory tests. Regarding the medical anamnesis a detailed life-long occupational history was taken with information of types of solvents used together with general conditions of hygiene at work. A cumulative exposure index was calculated using the number of hours of work with degreasing or other direct solvent exposure per week, multiplied by the number of years of exposure, multiplied by 45 working weeks per year. From this estimation of the total number of exposure hours, the study group was divided into four groups with nearly equal numbers of persons: group I (reference group) less than 1 year, group II 1–2.8 years, group III 2.9–6.7 years, and group IV 6.8–35.6 years of full-time exposure. Exposure data are presented in terms of these groups in Table 2. In Table 3 the same cumulative exposure is analyzed as a continuous variable. In Table 4 acute effects are studied with exposure categories of present exposure in hours/week, still based on the medical interview.

The dominant exposure for 70 workers in our study group was trichloroethylene (mean exposure time 7.1 years, 25.0 h per week),

and for 25 persons it was CFC 113 (mean exposure time of 4.2 years, 15.1 h per week). Present or recent exposure to trichloroethylene was quantified by blood and urine analyses of the metabolites trichloroacetic acid (TCA) and trichloroethanol. The mean urine TCA in the highest exposure group was 7.7 mg, with a maximum TCA of 26.1 mg/l. However, historical exposure data, reviewing all measurements of TCA in urine, notified to the Danish Labor Inspection Service during the period 1947–1987, indicate a fairly constant and high exposure level corresponding to about 40–60 mg/l urine TCA from the mid 1950s to the mid 1970s, which is the time period relevant to this study population [3].

All metal degreasers worked separately from metal processing and were considered not to have been exposed to metals such as cadmium and nickel. A 10-ml blood sample was taken from an antecubital vein, and urine samples were taken from morning urine. Both blood and urine samples were stored at −20°C until analysis was conducted. Determination of liver function tests was carried out by conventional methods (Boehringer Biochemia and Technicon). Urinary NAG activity was measured in duplicates with a fluorometric assay using 4-methyl-umbelliferyl-*n*-acetyl-β-glucosaminidase as substrate [8, 13]. NAG activity values were expressed as released 4-methylumbelliferone (μmol) per hour per gram urinary creatinine. Urinary creatinine content was measured as a standard kinetic picric acid assay, and the values used for correction of NAG activity for urine flow differences. The varying number of subjects in Table 1 relate to sufficient usable test material.

Reference values for liver function activity and the single kidney test were those commonly used by our laboratory. None of the study population had any previous or present clinical liver or renal disease, and none was taking known hepato- or nephrotoxic drugs.

The most relevant confounding variables of this study were found to be age and alcohol abuse. In the multivariate analysis, which allows for control of confounding variables, age is considered as a continuous variable. The limit for alcohol abuse was chosen as a weekly consumption of more than 21 drinks or periods as an alcoholic, defined as periods with treatment for alcohol abuse. This was the case for five persons. Alcohol abuse was used as a dichotomous variable in the multiple regression.

The statistical assessment involved linear and multiple regression analyses and analysis of variance. The material was also analyzed with exposure variables after logarithmic transformation – the non-log variables giving the best fit.

Results

Table 1 shows mean values from liver and kidney tests for all the exposed workers. Table 2 presents the dose-response relationship in the four groups of increasing cumulative exposure to all organic solvents, the predominant solvent being trichloroethylene. To maximize the power of the linear regression as shown in Table 2, this analysis is based on continuous values of exposure and effect variables. The dose-response relationship was statistically significant for two parameters, γ-glutamyltransferase (GGT) and NAG. For these liver and kidney function tests, respectively, a multiple regression analy-

Table 1. Mean levels of six liver and one kidney function tests for the total group of exposed workers

	Reference values and units[a]	Study group			
		Mean	SEM	Range	*n*
Serum ASAT	10–40 u/l	21.9	0.72	8 – 52	96
Serum GGT	10–40 u/l	30.8	3.5	2 –183	94
Serum alkaline phosphatase	80–250 u/l	156.6	3.9	63 –256	98
Serum bilirubin (total)	< 22 μmol/l	8.2	0.36	2 – 23	97
Serum protein (total)	60–78 g/l	70.4	0.45	60 – 84	98
Plasma prothrombin	0.80–1.20 u/l	0.96	2.3	0.12– 1.3	98
Urine NAG	30–60 u/g creatinine	53.6	3.9	11.2 –193.8	85

ASAT, Aspartate aminotransferase. NAG activity u/g creatinine = μmol 4-methylbelliferone $h^{-1}g^{-1}$ urinary creatinine

[a] Liver enzymes = enzyme units/liter

Table 2. Mean levels of liver and kidney tests in four groups of increasing cumulative solvent exposure

	Exposure groups[a]				Linear regression[b]	
	I ($n = 23$)	II ($n = 25$)	III ($n = 26$)	IV ($n = 26$)	Slope	*P*
Serum ASAT (u/l)	21.3	23.6	20.5	22.2	0.1	0.91
Serum GGT (u/l)	16.2	32.4	26.7	44.6	−6.3	0.03
Serum alkaline phosphatase (u/l)	162.5	158.8	148.2	157.2	. 1.7	0.61
Serum bilirubin (μmol/l)	8.6	7.8	9.0	7.5	−0.1	0.68
Serum protein (g/l)	71.0	70.9	69.7	70.1	−0.4	0.29
Plasma prothrombin (u/l)	94.9	98.2	97.0	94.8	−1.3	0.53
Urine NAG (u/g creatinine	42.7	51.4	51.8	65.1	6.2	0.05

ASAT, Aspartate aminotransferase

[a] Number of years of full time exposure mean (range): group I, 0.6 (0–0.99); group II, 1.9 (1–2.8); group III, 4.4 (2.9–6.7); group IV, 14.4 (6.8–35.6)

[b] Linear regression analysis (calculation of deviation of mean values from horizontal slope refers to the effect of 10^4 h of cumulative exposure). The linear regression was made on continuous exposure and effect variables

Table 3. Multiple regression analysis of the two tests with significant bivariate association to cumulative solvent exposure, serum GGT and urinary NAG activity

	Serum GGT						Urinary NAG					
	Bivariate			Multivariate			Bivariate			Multivariate		
	α	β	*P*	α	β	*P*	α	β	*P*	α	β	*P*
	24.8			4.4			47.0			40.6		
Solvent exposure		−6.3	0.03		−4.6	0.13		6.2	0.05		5.4	0.11
Age					0.5	0.08					0.18	0.61
Alcohol abuse					27.7	0.07						

α, Intercept; β, slope/intercept for solvent exposure and covariates; *P*, significance, test for no effect of covariate (β = 0). For the two continuous covariates, β refers to the effect of 10^4 h of exposure and 1 year of age.

Table 4. Urinary NAG activity by groups of present exposure (h/week) and peak exposure of solvents

Exposure groups	Urinary NAG			Analysis of variance	
	Mean	SD	*n*	*F*	*P*
Present exposure to all organic solvents					
1– 5 h/week	49.0	26.7	13		
6–29 h/week	46.2	28.9	25		
30–50 h/week	63.3	27.5	14	1.7	0.19
Present exposure to trichloroethylene					
1– 5 h/week	43.4	19.5	10		
6–29 h/week	57.5	43.2	7		
30–50 h/week	64.8	34.7	8	1.0	0.37
Peak exposure[a]					
− Peak	45.9	30.0	61		
+ Peak	72.4	44.1	25		0.009

[a] Peak exposure > 30 h/week in 1 year, *t*-test

sis was carried out with age and alcohol abuse as confounding variables in relation to GGT and age in relation to NAG (Table 3). This resulted in nonsignificant relationships between solvent exposure and the two parameters, especially concerning GGT, the two confounding variables accounting for a considerable proportion of the variance.

The knowledge of toxicodynamics and exposure characteristics between toxic substances and NAG is still insufficient. Therefore we proceeded by testing the association with present and peak solvent exposure (Table 4), which suggested a weak relationship. The marked difference for peak exposure may be explained partly by the presence of many long-term exposed workers in this group.

Discussion

The biomonitoring of liver function of subjects occupationally exposed to hepatotoxic substances currently involves an unsolved problem. Some newer studies have recommended the determination of serum bile acid concentration, but the findings can not be considered as unequivocal [5, 6]. In the present study, a battery of traditional liver tests have been used covering a variety of functions. In the bivariate analyses there seemed to be a dose-response relationship between long-term solvent exposure and an increase in GGT activity. After controlling for the effect of age and alcohol, the association between solvent exposure and enzyme activity was, however, considerably weaker and nonsignificant. This is in accordance with a recent study in Taiwan among xylene-exposed spray painters, which also found GGT to be a sensitive parameter of liver screening at the subclinical level [2]. In the latter study GGT activity increased independently with increased alcohol consumption and solvent exposure [2].

Studies involving heavy-metal poisoning have established that urinary enzymes are the most sensitive indicators of renal damage [9, 10]. However, there are also reports of small but significant rises in urinary enzyme activity after long-term, moderate occupational exposure to mercury, lead, cadmium, and solvents [1, 4, 12].

Autoimmune glomerulonephritis is considered the most conclusive case of a relationship between solvent exposure and renal disease, while tubular enzyme studies are still placed at the experimental stage [4]. Urinary NAG activity seems to be the most applicable enzyme parameter [7].

The present study indicates that subclinical tubular dysfunction is associated with long-term and peak exposure to degreasing solvents. However, multiple regression failed to demonstrate a significant relationship. There was even more weak and insignificant signs of acute effects in relation to present solvent exposure. The assessment of early tubular dysfunction by urinary enzymes is still at the research stage. NAG has proven to be one of the most valuable enzymes, with the advantages of stability in urine and a high level of activity in the kidney. However, more epidemiological work is needed to determine the sensitivity and specificity of NAG.

In conclusion, this study examined metal degreasers who had undergone long-term exposure mainly to trichloroethylene, previously at levels around the threshold limit value and presently at substantially lower levels. A battery of liver tests and one renal tubular test indicated a (nonsignificant) association with solvent exposure.

Acknowledgements. The study was supported by grants from the Danish Medical Research Council and Sygekassernes Helsefond.

References

1. Bernard AM, Roels H, Cardenas A, Lauwerys R (1990) Assessment of urinary protein 1 and transferin as early markers of cadmium nephrotoxicity. Br J Ind Med 47:559–565
2. Chen JD, Wang JD, Jang JP, Chen YY (1991) Exposure to mixtures of solvents among paint workers and biochemical alteriations of liver function. Br J Ind Med 48:696–701
3. Christensen JM, Rasmussen K (1990) The exposure of Danish workers to trichloroethylene 1947–1987 (in Danish). Ugeskr Laeger 152:464–467
4. Franchini I, Cavatorta A, Falzoni M, Lucertini S, Mutti A (1983) Early indicators of renal damage in workers exposed to organic solvents. Int Arch Occup Environ Health 52:1–9
5. Franco G (1991) New perspectives in biomonitoring liver function by means of serum bile acids: experimental and hypothetical biochemical basis. Br J Ind Med 48:557–561
6. Franco G, Fonte R, Tempini G, Canduar F (1986) Serum bile acid concentrations as a liver function test in workers occupationally exposed to organic solvents. Int Arch Occup Environ Health 58:157–164
7. Lauwerys RR, Bernard A (1987) Early detection of nephrotoxic effects of industrial chemicals. State of the art and future prospects. Am J Ind Med 11:275–285
8. Meyer BR, Fishbein A, Rosenman K, Lerman Y, Drager DE, Reidenberg MM (1984) Increased urinary enzyme excretion in workers exposed to nephrotoxic chemicals. Am J Med 76:989–998
9. Price RG (1982) Urinary enzymes, nephrotoxicity and renal disease. Toxicology 23:99–134
10. Stonard MD, Gore CW, Oliver GJA, Smith IK (1987) Urinary enzymes and protein patterns as indicators of injury to different regions of the kidney. Fundam Appl Toxicol 9:339–351
11. Torkelson TR, Rowe VK (1981) Halogenated aliphatic hydrocarbons containing chlorine, bromine and iodine. In: Clayton GD, Clayton FE (eds) Patty's industrial hygiene and toxicology. Wiley-Interscience, New York 3433–3601
12. Verschoor M, Herber R, Hemmen JV, Wibowo A, Zielhuis R (1987) Renal function of workers with low-level cadmium exposure. Scand J Work Environ Health 13:232–238
13. Yuen C-T, Price RG, Chattagoon L, Richardson AC, Praill PFG (1982) Colorimetric assays for *N*-acetyl-beta-D-glucosaminidase and beta-D-galactosidase in human urine using newly-developed ω-nitrostyrol substrates. Clin Chem Acta 124:195–204

Int Arch Occup Environ Health (1988) 60:419–423

International Archives of
Occupational and Environmental Health

A genotoxic study of metal workers exposed to trichloroethylene

Sperm parameters and chromosome aberrations in lymphocytes

Kurt Rasmussen[1], Svend Sabroe[1], Mogens Wohlert[2], Hans J. Ingerslev[2], Birgitte Kappel[3], and Johannes Nielsen[3]

[1] Institute of Social Medicine, University of Aarhus, Aarhus, Denmark
[2] Department of Gynecology and Obstetrics, Århus Kommunehospital, Aarhus, Denmark
[3] Laboratory of Cytogenetics, Psychiatric Hospital, Risskov, Aarhus, Denmark

Summary. Metal workers exposed to trichloroethylene for the degreasing of metals were studied to evaluate the genotoxicity of this exposure. For 15 workers presently exposed to high doses of trichloroethylene there was no difference from unexposed persons with respect to sperm count and morphology, and a small increase of two fluorescent bodies (YFF%) in spermatozoa. In contrast, there was a highly significant increase in frequency of structural aberrations (breaks, gaps, translocation, deletions, inversions) and hyperdiploid cells in cultured lymphocytes from trichloroethylene degreasers. As control groups, physicians from chemically non-exposed surroundings and a concurrently sampled reference from cytogenetic investigations were used. This study indicates positive correlations between exposure to trichloroethylene and somatic chromosome aberrations, whereas no effect on male germ cells could be demonstrated.

Key words: Trichloroethylene – Metal workers – Sperm morphology – YFF sperm analysis – Chromosome damage

Introduction

Increasing evidence suggests a reproductive risk related to physical and chemical toxins. The contribution of occupational exposure of male workers to reduced fertility is of interest, because they are often more heavily exposed than female workers.

Offprint requests to: K. Rasmussen, Clinic of Occupational Medicine, Århus Kommunehospital, DK-8000 Aarhus C, Denmark

Throughout the last decade, studies have indicated that lead, vinyl chloride, dibromochloropropane (DBCP) and cytostatic agents may affect sperm cell formation and induce chromosome aberrations (Lancranjan et al. 1975; Heath et al. 1977; Kapp and Jacobsen 1980; Nikula et al. 1984). The nematocide DBCP is probably the most studied chemical agent concerning male genotoxicity. Several studies of this agent have shown a decrease in sperm count and increased frequency of double Y bodies in sperm, which may indicate Y-chromosomal non-disjunction (Glass et al. 1979; Kapp and Jacobsen 1980). Epidemiological studies on the reproductive outcome of paternal exposure to hydrocarbons have been inconclusive (Strobino et al. 1978).

Trichloroethylene is used as an industrial solvent for the degreasing of metals, drycleaning, and as a solvent for organic products. It is estimated that 3.5 million workers world wide are exposed to this agent (Dekant et al. 1984).

The aim of this study is to evaluate the genotoxicity in a group of metal workers exposed to high doses of trichloroethylene. The parameters studied are sperm count and morphology, the spermatozoa Y-chromosomal non-disjunction of the Y-chromosome during spermiogenesis and chromosomal aberrations in cultured lymphocytes.

Material and methods

The study population consisted of all identifiable metal degreasers from a well-defined geographical area corresponding to the county of Århus, Denmark. They were exposed to either trichloroethylene or fluorocarbon 113. Out of 116 ex-

posed workers in active employment, 99 participated. They went through a one day clinical examination programme at a hospital department for occupational medicine.

In the genotoxic examinations only workers degreasing with trichloroethylene for more than 20 h per week were included. Fifteen workers fulfilled this criterion, actively degreasing until the day of examination. They comprise the population in this study. All the degreasing plants were half open vapour plants. Data on exposure, confounding factors etc. were collected by occupational medical interview.

Whole blood samples were handled according to standard techniques, and incubated at 37°C in a closed system for 48 h (Friedrichs and Nielsen 1973). Medium 199 (Earls' BBS) was used as culture medium. The metaphases were stained with BUDR-acridine orange (Friedrichs and Nielsen 1973). For all but four individuals, 100 metaphases were analysed for unstable (transient) chromosome aberrations: structural aberrations, and hyperdiploid cells. We scored breaks, gaps, translocations, deletions and inversions as structural aberrations. A break was classified as such when the distal segment of the chromatid was clearly separated from the rest of the chromatid; otherwise it was considered a gap. Chromatid type and chromosome type changes were scored additively. Hyperdiploid cells are cells with more than 46 chromosomes. As reference material a concurrently sampled group from a population study, and parents of offspring with stable chromosome abnormalities found in an ongoing survey in the same area were used (Nielsen et al. 1982). This group comprised 669 persons with 7889 metaphases being analysed.

Of the 15 workers asked to deliver a semen specimen, 13 accepted, and samples were delivered at the laboratory within 1 h after ejaculation. The time span elapsed since the penultimate ejaculation was recorded.

The semen examination was performed essentially as recommended by WHO (1980). Analyses were made for common quality parameters: count, volume, motility, and morphology. Air-dried slides were stained with quinacrine dihydrochloride. A minimum of 500 sperm was scored for each sample. The proportion of mature spermatozoa containing zero, one or two fluorescent Y-bodies was determined. The presence of two fluorescent bodies (YFF%) in a normal-sized spermatozoa may indicate the presence of two Y-chromosomes resulting from a chemically induced event during the second reduction division. The method and scoring criteria described by Kapp and Jacobsen (1980) were used. Fourteen non-exposed physicians working at university institutions served as controls. The mean age of the exposed group was 35.5 years (range 20–62) compared to 36.3 years (range 29–42) in the control group. The Mann-Whitney Rang sum test, χ^2 test and one-way analysis of variance were used in the statistical analysis.

Results

The result of sperm count and morphology is presented in Table 1. No marked differences were observed.

One of the 13 exposed workers was azoospermic in repeated samples. Testis biopsy confirmed normal spermiogenesis, while explorative surgery revealed bilateral aplastic ductus deferens, which was regarded as congenital. A 20-year-old man had been operated for cryptorchidism at the age of 12. His spermiogram showed a normal sperm count, reduced motility and 60% abnormal heads.

Table 2 shows an increased but statistically insignificant frequency of YFF cells in the exposed group. There was little interindividual variation of the percentage of YFF cells among degreasers. Only one of the workers was an outlayer. He showed an YFF-value of 5.7% – a level corresponding to findings in studies with known genotoxic exposure.

In Table 3 absolute numbers are given of chromosome aberrations in the exposed group. The number

Table 1. Sperm quality

	Sperm count mill/ml		% abnormal heads	
	Mean	Range	Mean	Range
Exposed group ($n = 12$)	95.8	(27–164)	34.8	(20–60)
Control group ($n = 14$)	70.3	(34–159)	32.1	(25–50)
p-value[a]	>0.10		>0.10	

[a] Mann-Whitney Rang-sum test

Table 2. YF and YFF frequencies in exposed and control group

	Sperm cells analysed n	YFF cells n	YF% Mean	YF% 95% confidence interval	YFF%[a] Mean	YFF%[a] 95% confidence interval
Exposed group ($n = 12$)	7472	126	45.2	(43.7–46.8)	1.7	(1.4–2.0)
Control group ($n = 14$)	7396	103	44.8	(43.3–46.3)	1.4	(1.1–1.7)
p-value[b]			>0.10		>0.10	

[a] $\frac{\text{YFF}}{\text{XX} \times \text{XY}} \times 100$

[b] Mann-Whitney Rang-sum test

Table 3. Unstable chromosome aberrations in the exposed group

Person	Analysed metaphases	Gaps		Breaks		Sum of translocations, deletions and inversions		Hyperdiploid cells	
	n	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
1	29	6	(20.7)	0	(0.0)	0	(0.0)	0	(0.0)
2	37	0	(0.0)	0	(0.0)	1	(2.7)	0	(0.0)
3	47	6	(12.8)	0	(0.0)	0	(0.0)	0	(0.0)
4	48	28	(58.4)	4	(8.3)	2	(4.2)	1	(2.1)
5	100	15	(15.0)	0	(0.0)	1	(1.0)	0	(0.0)
6	100	16	(16.0)	0	(0.0)	4	(4.0)	3	(3.0)
7	100	18	(18.0)	1	(1.0)	0	(0.0)	0	(0.0)
8	100	14	(14.0)	5	(5.0)	3	(3.0)	1	(1.0)
9	100	12	(12.0)	1	(1.0)	1	(1.0)	1	(1.0)
10	100	13	(13.0)	0	(0.0)	0	(0.0)	0	(0.0)
11	100	19	(19.0)	2	(2.0)	2	(2.0)	1	(1.0)
12	100	15	(15.0)	4	(4.0)	0	(0.0)	0	(0.0)
13	100	58	(58.0)	2	(2.0)	1	(1.0)	0	(0.0)
14	100	42	(42.0)	4	(4.0)	1	(1.0)	2	(2.0)
15	100	11	(11.0)	1	(11.0)	1	(1.0)	1	(1.0)
Total	1261	273		24		17		10	

Table 4. Unstable chromosomal aberrations in exposed and control group

	Exposed group ($n = 15$)		Control group ($n = 669$)		p-value[a]
	Mean (%)	95% confidence interval	Mean (%)	95% confidence interval	
Number of metaphases analysed	1261		7889		
Gaps	21.66	(19.17–24.40)	2.80	(2.44–3.20)	<0.001
Breaks	1.90	(1.22– 2.84)	0.85	(0.66–1.08)	<0.001
Sum of translocations, deletions and inversions	1.35	(0.79– 2.16)	0.15	(0.08–0.27)	<0.001
Hyperdiploid cells	0.79	(0.38– 1.46)	0.24	(0.15–0.38)	0.0013

[a] χ^2-test

Table 5. Number of persons in the exposed group with chromosomal coalterations

Gaps	Breaks	Hyperdiploid cells	Structural abnormalities	Number of persons
×	×	×	×	6
×	×		×	1
×		×	×	1
×	×			2
×			×	1
×				3
			×	1

Table 6. Multialterations. Semen alterations in relation to few/many chromosome aberrations

Chromosome alterations	YFF%	Abnormal heads (%)
1–2	1.1	32.0
3–4	2.0	36.9
p-value[a]	0.31	0.55

[a] F-test. Analysis of variance

of gaps for person nos. 4, 13 and 14 is considerably higher compared to the rest of the group. These three metal workers all have been full time degreasers for periods of 9, 2 and 3 years respectively, and with some of the highest values for urine content of trichloroethylene as an expression of a relatively high present exposure. In Table 4 a comparison is made to the reference group showing fairly high and strongly significant increased frequencies in the exposed group, especially with respect to gaps and structural aberra-

Table 7. Chromosome aberrations and sperm alterations in relation to exposure

Exposure to trichloroethylene	Gaps (%)	Breaks (%)	Hyper-diploids (%)	Structural abn. (%)	YFF (%)	Abnormal heads (%)
Full-time (40 h/w) ($n = 8$)	30.7	23.3	0.71	0.86	1.69	38.6
Part-time (20 h/w) ($n = 7$)	13.8	15.0	0.63	1.38	1.61	29.6
p-value[a]	0.05	0.53	0.86	0.42	0.94	0.26
$n =$	15	15	15	15	12	12

[a] Analysis of variance. F-test

tions. The mean percentages in Table 4 are simple, not weighed, mean values.

From Table 5 there appears an accumulation of coalterations, i.e. the same persons tend to have more than one type of chromosomal aberration. Table 6 shows the highest proportion of Y-chromosomal non-disjunction and abnormal heads in the groups with most chromosomal aberrations but the difference was not significant. In an attempt to evaluate the importance of the intensity of exposure, a dichotomization was made between the full and part time degreasers (Table 7). Those working full-time with degreasing seem to produce more gaps and breaks.

As possible confounding factors we explored evidence for X-ray examination, febrilia, viral disease during the last three months prior to sampling, and alcohol consumption. In a bivariate analysis among the exposed, these potential confounders were found not to be positively or negatively correlated to the effect measures. Three of the 15 trichloroethylene degreasers were actually taking drugs. However, none of these were suspected mutagenic.

Discussion

In recent studies reduced fertility has been shown among painters (Bjerrehus and Detlefsen 1986). This may be due to sexual impotence and reduced sexual activity related to the cerebral effect of solvent exposure. However, mutagenic or toxic activity might also play a role.

In this study we found no differences in sperm count and morphology, and an insignificantly increased frequency of YFF% in a trichloroethylene exposed group, compared to a reference group of non-exposed medical doctors. The mean YFF% in the reference group is in accordance with values from other recent studies, where a YFF% of 1.2 to 1.6 has been reported (Kapp and Jacobsen 1980; Ward et al. 1984). Studies of individuals exposed to antineoplastic agents, radiation therapy, and small groups exposed to the nematocide DBCP have shown a 2 to 4-fold increased incidence of YFF-sperm. However, all presently published reports deal with very small numbers of study populations.

In contrast to the negative result in the germ cell study we found a highly significant increase of unstable chromosome aberrations among trichloroethylene degreasers. The reference group is not ideal. It consisted partly of survey investigations of groups of the normal population (session material and school children) and partly of parents of offspring with stable chromosome alteration. In the reference group, information on confounding factors such as viral infection, X-ray, alcohol and workplace mutagenic exposure was not available. There is, however, no reason to believe that the distribution of these confounding factors should differentiate this fairly big reference material of 669 persons from the average population. Should there be confounding, we cannot tell in which direction, unless parents of offspring with stable chromosome alteration should have an increased frequency of unstable chromosome alterations. Such confounding would tend to underestimate the actual increased risk of mutagenic findings in the occupationally exposed groups.

The increased prevalence of structural aberrations and hyperdiploid cells in the exposed group corresponds to results of a Danish investigation of 28 laboratory technicians (Wohlert et al. 1986). However, the frequency of gaps, albeit a minor aberration, is much higher in the present study (21.8% compared to 7% among the laboratory workers). It must be pointed out that all these aberrations were scored in cells with 46 chromosomes per cell.

In a small Chinese study of six workers using trichloroethylene for metal degreasing, a statistically significant increase in the rate of sister-chromatid exchange was found compared to parallel controls (Gu et al. 1981).

Trichloroethylene is one of the most frequently tested organic solvents in short-term mutation tests. Of the approximately 100 tests available today, trichloroethylene has been examined in 18 systems –

with a positive result in 13 (Vainio et al. 1985). Epidemiological studies have not shown any increased incidence of cancer or cancer mortality after exposure to trichloroethylene (Axelson et al. 1978).

Unstable chromosomal aberrations in cultured, circulating lymphocytes are regarded as a reliable indicator of mutagenic exposure (Carrano 1986). Induced cytogenetic damages must be anticipated to be low in occupational settings, because relevant exposures are often repeated but at a fairly low dose. Lymphocytes reflect the phenomenon of cumulative exposure, having half lives between 12 months and 20 years. We do not know clearly the health consequence of increased chromosome damages in somatic cells. On the other hand, this study tends to show an association between exposure and damage. Looking at the sub-group working full-time with trichloroethylene degreasing, there are evidently more chromosome aberrations than in the rest of the exposed group degreasing 20 h per week, and typically painting the rest of the time. The full-time degreasers were not exposed to any chemicals other than trichloroethylene. An expression of the exposure strain of this group of metal degreasers can be found in the urine content of trichloroacetate (U-TCA), as an indicator of present exposure, and occupational history data of cumulative exposure. The mean U-TCA for the 15 workers was 3.7 mg/l (range 0.02–26.9), which is fairly low (the guiding WHO limit value is 50 mg/l). The cumulative exposure calculated in full working years with trichloroethylene was 4.6 years (range 0.8–22.0).

This study indicates mutagenic effects after trichloroethylene exposure. Further studies on YFF sperm determination in larger exposed groups and metaphases analyses on sperm cells are advisable in order to obtain a better knowledge of the correlation between somatic and germ cell chromosomal alterations.

Acknowledgements. This work was supported by grants from the Danish Medical Research Council and Sygekassernes Helsefond.

References

Axelson O, Andersson K, Hogstedt C, Holmberg B, Molina G, Deverdier A (1978) A cohort study on trichloroethylene exposure cancer mortality. J Occup Med 20:194–196

Bjerrehus T, Detlefsen GV (1986) Infertility in Danish painters exposed to organic solvents. Ugeskr Laeger 148:1105–1106 (in Danish)

Carrano AV (1986) Chromosomal alterations as markers of exposure and effect. J Occup Med 28:1112–1116

Dekant W, Metzler M, Henschler D (1984) Novel metabolites of trichloroethylene through dechlorination reactions in rats, mice and armans. Biol Pharmacol 33:2021–2027

Friedrichs V, Nielsen J (1973) Chromosome studies in 5,049 consecutive newborn children. Clin Genet 4:333–343

Glass RI, Lyness RN, Mengle DC, Powell KE, Kahn Z (1979) Sperm count depression in pesticide applicators exposed to dibromochloropropane. Am J Epid 109:346–351

Gu ZW, Sele B, Chmara D et al. (1981) Effects of trichloroethylene and its metabolites on the rate of sister-chromatic exchange. In vivo and in vitro study on the human lymphocytes. Ann Génét 24:105–106 (in French)

Heath CW, Dumont CR, Gamble J, Waxweiler R (1977) Chromosomal damage in men occupationally exposed to vinyl chloride monomer and other chemicals. Environ Res 14:68–72

Kapp RW, Jacobsen CB (1980) Analysis of human spermatozoa for Y-chromosomal non-disjunction. Teratog Carcinog Mutag 1:193–211

Lancranjan I, Popescu HI, Gavanescu O, Klepsch I, Serbanescu M (1975) Reproductive ability of workmen occupationally exposed to lead. Arch Environ Health 30:396

Nielsen J, Wohlert M, Faaborg-Andersen J, et al. (1982) Incidence of chromosome abnormalities on newborn children. Comparison between incidences in 1969–1974 and 1980–1982 in the same area. Hum Genet 61:98–101

Nikula E, Kiviniitty K, Leisti J, Taskinen PJ (1984) Chromosome aberrations in lymphocytes of nurses handling cytostatic agents. Scand J Environ Health 10:71–74

Strobino B, Kline R, Stein Z (1978) Chemical and physical exposure of parents: effects on human reproduction and offspring. Early Hum Dev 1/4:371–399

Vainio H, Waters MD, Norppa H (1985) Mutagenicity of selected organic solvents. Scand J Work Environ Health [Suppl 11] 1:75–82

Ward JB, Hokanson JA, Smith ER, Chang LW, Pereira MA, Wharton EB, Legator MS (1984) Sperm count, morphology and fluorescent body frequency in autopsy service workers exposed to formaldehyde. Mutat Res 130:417–424

Wohlert M, Nielsen J, Johansson M (1986) Cytogenetic and occupational medical investigation of 28 laboratory technicians in a research laboratory. Ugeskr Laeger 148:578–581 (in Danish)

World Health Organization (1980) Laboratory manual for the examination of human semen and semen-cervical mucus interaction. Press Concern, Singapore, pp 1–43

Received October 20, 1987 / Accepted February 5, 1988

ORIGINAL MEDDELELSE

Danske arbejderes udsættelse for triklorætylen 1947-1987

Cand. scient. Jytte Molin Christensen & Kurt Rasmussen

De klorerede opløsningsmidler gjorde deres entre med den industrielle revolution i slutningen af 1800-tallet. Tetraklorkulstof var den første klorerede kulbrinte, der fremstilledes i større mængde til industrielle formål. Men på grund af tetraklorkulstofs toksicitet blev stoffet fortrængt af triklorætylen, der er fremstillet industrielt fra omkring 1910. Det nye stof blev hurtigt brugt som affedtningsmiddel i maskinindustrien og som opløsningsmiddel for organiske produkter. Fra omkring 1935 blev triklorylen anvendt til inhalationsanæstesi inden for sygehusvæsenet, især i ortopædkirurgien, en anvendelse der dog var gledet ud mod slutningen af 1970'erne. Andre anvendelsesområder er kemisk tøjrensning, som opløsningsmiddel i den farmaceutiske industri og som indholdsstof i lim og lak (1).

Forbruget af triklorætylen steg stærkt især fra 1950'erne og op til midt i 1970'erne. Herefter skete det næste større skred i substitutionen af klorerede opløsningsmidler, denne gang med substitution til mindre toksiske produkter som 1,1,1-trikloætan og freonprodukter eller endog substitution til vandbaserede affedtningsmidler.

Det årlige forbrug af triklorætylen i Danmark er nu på ca. 2.000 tons. Omkring 5.000 danske arbejdere skønnes at være dagligt eller jævnligt eksponerede. På verdensplan skønnes det, at antallet af eksponerede arbejdere er ca. 3,5 mio.

Triklorætylen metaboliseres til trikloreddikesyre og triklorætanol, der udskilles gennem nyrerne. Ved måling af trikloreddikesyre i urinen kan man få et billede af det eksponeringsniveau, der har været gældende primært i de nærmest forudgående 1-7 dage. En sådan biologisk monitorering af arbejdere udsat for triklorætylen ved hjælp af løbende helbredsovervågning har været anvendt på en del danske arbejdspladser siden 1947.

Formålet med denne artikel er at beskrive den historiske udvikling i eksponeringsniveauet for danske arbejdere eksponeret for trikloætylen 1947-1987. Som supplement gengives sygehistorier for den tidligste del af perioden.

EGNE UNDERSØGELSER

MATERIALE OG METODER

Gruppen af klorerede opløsningsmidler (halogenerede kulbrinter) omfatter en lang række stoffer. De 5 der anvendes i størst mængde, er: Triklorætylen (TRI), 1,1,1-triklorætan, tetraklorætylen, metylenklorid og klorfluorkarboner (freoner) (1).

Omkring 70% af den mængde TRI, der optages i organismen, metaboliseres. Ca. 50% udskilles i urinen som triklorætanol (TCE) med en halveringstid på 10-15 timer, medens 10-30% udskilles som trikloreddikesyre (TCA). Da TCA i organismen er bundet til plasmaproteiner, udskilles det langsomt via nyrerne med en halveringstid på omkring 100 timer (2-4). TCA har således en tendens til at akumuleres i kroppen. Urin-TCA er den bedste parameter til at udtrykke eksponering for halogenerede kulbrinter inden for den sidste måned. Ved en gennemsnitlig eksponering på 30 parts per million (ppm) triklorætylen i løbet af 4-5 timer fås en TCA-værdi på normalt 65-80 mg/l (5).

Af de øvrige halogenerede kulbrinter sker der kun metabolisering til TCA for 1,1,1 triklorætan og perklorætylen og her kun i meget beskedent omfang (1-2% af den optagne mængde). Biologisk monitorering af eksponerede arbejdere er således i praksis kun af værdi for dem, der er beskæftiget med triklorætylen.

I perioden 1947-1986 er der generelt sket en hurtig teknisk udvikling af målemetoder og analyseydstyr, således at metoderne generelt i dag er mere specifikke og nøjagtige. Dette er også tilfældet for måling af opløsningsmiddeldampe i luft (6), mens metoden til måling af TCA i urin har været uændret i hele opgørelsesperioden (7, 8). Det drejer sig om Fujiwara-metoden, der er diagnostisk uspecifik, men som er hurtig og simpel og har en god analytisk nøjagtighed og derfor er anvendelig i screeningsøjemed. Fujiwara-metoden er baseret på en reaktion mellem TCA og pyridin i alkalisk opløsning ved 65°C (9, 10). Reaktionsproduktet kan måles spektrofotometrisk ved 530 nm. Mekanismen for denne reaktion er stadig ikke helt opklaret.

Metoden er ligeledes sammenlignelig med en ny enzymatisk gaskromatografisk metode, og der findes god overensstemmelse ved eksponering for »rene« halogenerede carbonhydrider, hvilket bekræfter, at Fujiwara-metoden er uspecifik og derfor kun anvendelig som screeningmetode (11).

Måling af TCA i urinen blev indført i Danmark i 1947. Oplysningerne er samlet på Arbejdstilsynets centrale forsknings- og målelaboratorium. Fra 1947 til 1954 hed det Fabriks- og Arbejdstilsynets laboratorium, herefter Statens Institut for Arbejdshygiejne frem til 1977 og siden da Arbejdsmiljøinstituttet (AMI).

Arbejdstilsynets målerapporter vedrørende TCA er gennemgået for perioden 1947-88. For hvert måleresultat er der registreret måletidspunkt, branche og virksomhed. Der er registreret i alt 2.272 målinger på 330 forskellige virksomheder i perioden 1947-1986. Brancherne er kodet efterfølgende opdeling: Metalindustrien (affedtning), kemiske tøjrenserier, trykkerier, hospitaler (anæstetikum), medicinsk og kemisk industri samt møbelindustri. Materialet er statistisk bearbejdet med programpakken Minitab.

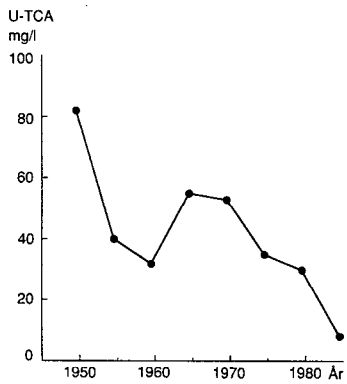


Fig. 1. *Biologisk belastning af triklorætylen hos danske arbejdere 1947-1987. Gennemsnitsværdier af trikloreddikesyre i urinen (U-TCA), opdelt i 5-års perioder.*

Arbejdsmiljøinstituttet, København, og
Arbejdstilsynet, Kreds Århus Amt.

Tabel 1. *Danske arbejdere udsat for triklorætylen 1947-1987. Måleresultater for trikloreddikesyre i urin, mg/l.*

Årstal	Antal målinger	Gennemsnitsværdi (middel)	Variationsbredde
1947-1951	398	82	0-750
1952-1956	438	40	0-1.975
1957-1961	247	32	0-680
1962-1966	254	55	0-730
1967-1971	553	53	0-850
1972-1976	104	35	0-370
1977-1981	185	30	0-365
1982-1986	108	18	0-130

Tabel 2. *Måleresultater for trikloreddikesyre i urinen (U-TCA)mg/l fordelt på brancher.*

Branche	Årstal	Antal virksomheder	Antal målinger	U-TCA gennemsnitsværdi	U-TCA variationsbredde
Metalindustri	1947-1986	147	1.544	48	0-1.975
Kemisk tøjrenseri	1947-1972	73	311	75	0-750
Trykkeri	1952-1982	6	57	17	0-250
Medicinal/kemisk industri	1950-1979	8	23	44	5-170
Hospitaler	1949-1980	1	1	730	730
Møbelindustri	1951-1970	6	17	110	5-280
Andet	1947-1986	51	210	70	0-740
Uoplyst	1947-1972	38	109	42	0-355
I alt	1947-1986	330	2.272	47	0-1.975

RESULTATER

Der er foretaget 2.272 målinger af TCA i urin. Måleresultater og antal opdelt på 5-års perioder er opført i Tabel 1 med angivelse af middelværdi og variationsbredde. De højeste koncentrationer er målt i perioden 1947-1974. Højeste værdi er fundet til 1.975 mg/l. I Fig. 1 er de beregnede middelværdier af de målte TCA-koncentrationer afsat mod måleperioden. Selv om der er større variationer, viser opgørelsen et tydeligt fald i TCA-koncentrationer gennem perioden. Det skal dog bemærkes, at gennemsnitbelastningen udtrykt ved disse biologiske målinger er på stort set samme niveau fra begyndelsen af 1950'erne til sidst i 1970'erne.

Tabel 2 viser måleresultaterne fordelt på brancher. I metalindustri og på tøjrenserier har henholdsvis 147 og 73 virksomheder deltaget i denne biologiske monitorering. Metalindustrien er den eneste branche, hvor der er repræsenteret målinger gennem hele 40-års perioden. En del virksomheder har deltaget regelmæssigt gennem 15-20 år, enkelte gennem hele perioden.

Fra ca. 1985/86 er der sket et brat fald, grænsende til ophør med brug af TCA-målinger. Grunden er formentlig først og fremmest fagforeningspolitisk og lægeetisk modstand mod biologisk monitorering på grund af risikoen for diskriminering af arbejdskraften.

Eksponerings- og sygehistorier beskrevet af Arbejdstilsynets læger

I. 1948, kemisk tøjrenseri

»Den 4 ds. undersøgtes på Arbejsmedicinsk Klinik en pressesvend, som for tiden er patient på Rigshospitalets neuromedicinske afdeling. Undersøgelsen dér har vist, at han bl.a. lider af en kronisk triklorætylenforgiftning. Han har deltaget i pasningen af anlægget til kemisk tøjrensning, hvor der renses med TRI. Det første halve år havde han ingen gener med arbejdet, men det sidste halve år fik han tiltagende hovedpine, som begyndte, når han havde været udsat for større mængder af TRI-damp, fx ved rensning af filterposerne, påfyldning af TRI og udtagning af gulvtæpper, som kun delvis kan tørres i apparatet. I tilslutning til hovedpinen har der været russornemmelse, abnorm arbejdstræthed, stærk søvnighed og glemsomhed og d. 20.12 havde han et større forgiftningstilfælde med bevidstløshed, hvorfor han blev indlagt på sygehuset i St. Heddinge og senere overflyttet til Rigshospitalet.«

II. 1948, dampppresseri

»*I virksomheden findes i et butikslokale ud imod gaden opstillet et dam*ppresseanlæg med kedel. I et baglokale til butikken foretages pletrensning med TRI i ret stort omfang. Tøjet anbringes på et bord, og fra en skål med TRI, der står på bordet, sker vaskning af pletter på tøj med en børste. Der beskæftiges ikke fremmed medhjælp, kun indehaveren og dennes hustru arbejder i virksomheden. Fabriksinspektøren havde henstillet til indehaveren at etablere afsugning ved TRI-arbejdet, men indehaveren mente ikke at have råd til at bekoste et sådant anlæg, hvorfor fabriksinspektøren nu ved den givne lejlighed ønsker udtaget en urinprøve af indehaveren og dennes hustru til laboratorieundersøgelse for TRI-urin. Da man kom ind i virksomheden havde indehaveren lige haft det uheld, at en flaske på ca. 10 l TRI var faldet på gulvet for ham og knust, så hele gulvet i baglokalet sejlede i TRI. Indehaveren forsøgte med en gulvklud at samle den spildte TRI op og vride kluden af i en gulvspand for at redde så meget som muligt. TRI-undersøgelsen viste følgende resultater: Indehaveren: 60 mg/l – indehaverens hustru: 550 mg/l.«

III. 1948, maskinværksted

»Ovennævnte arbejdsmand har i 27 år været ansat på maskinværkstedet, i perioder ved TRI-anlægget hvor han bl.a. har arbejdet de sidste 2 år. I de sidste 2 måneder har han haft anfald af uro, forvirrethed, voldsomme svedeture, søvnighed og alkoholintolerans. Han har været sygemeldt i 2 uger. Der påvistes intet abnormt ved den almindelige kliniske undersøgelse samt blodundersøgelse. Urinen viste et indhold af 255 mg trikloreddikesyre per l urin.«

IV. 1948, lynlåsfabrik

»Forskelligt arbejdsmandsarbejde i 17 år på ovennævnte virksomhed, de sidste 4 måneder ved TRI-renseanlægget. Fra den første dag ved dette arbejde var han generet af søvnighed under og efter arbejde, abnorm træthed og vægttab på 5½ kilo. Objektivt fandtes intet særligt, men urinen indeholdt 700 mg trikloreddikesyre per l.«

DISKUSSION

De data, der danner grundlag for denne opgørelse, har ikke været indsamlet systematisk blandt danske arbejdere eksponeret for triklorætylen eller blandt repræsentativt udvalgte. Det store fald i eksponeringsniveauet i 1980'erne er formentlig baseret på få og tilfældige målinger i en periode, hvor der har været en del røre om anvendelsen af biologisk monitorering. For så vidt det har kunnet efterspores, er initiativet til disse målinger på den enkelte virksomhed primært taget af Arbejdstilsynet, i mindre omfang af lokale læger, fx embedslæger. De samme virksomheder går igen fra år til år. Der er en tydelig geografisk skævdeling med ophobning i København, subsidiært på Sjælland.

Langt de fleste målinger vedrører arbejdere beskæftiget med metalaffedtning og tøjrensning, i overensstemmelse med den eksponeringsprofil der kendes fra andre oplysninger (1). Som opgørelsen viser, har triklorætylen dog også været anvendt til rensningsformål i den grafiske branche, som bedøvemiddel på hospitaler, som laboratoriemiddel i medicinal- og kemisk industri og som indholdsstoffer i lim på møbelfabrikker. Hertil kommer mere sjældne anvendelsesområder som gummifabrikation, dentalfabrikker, som indholdsstof i skocreme m.m.

Den eneste tidligere publicerede historiske opgørelse over opløsningsmiddelbelastning i Danmark vedrører den grafiske branche, hvor der er foretaget en opgørelse af forekomsten af opløsningsmiddeldampe i luften i perioden 1947-77 (6). Opgørelsen omfatter 347 målinger på 18 virksomheder. Der er fundet en tydeligt faldende trend i eksponeringsniveau, nogenlunde i overensstemmelse med eksponeringsniveauerne i den aktuelle opgørelse. Opgørelsen fra den grafiske branche er dog handicappet af i alt 7 forskellige måle- og analysemetoder.

Ved det svenske arbejdsmiljøinstitut har man foretaget en lignende opgørelse over trikloreddikesyreniveauet. Denne viste trikloreddikesyrekoncentrationer på ca. 1/10 i 1983 sammenlignet med koncentrationer i slutningen af 1950'erne. Der blev endvidere vist parallellitet mellem økonomiske opgangstider og høje trikloreddikesyreværdier, ligesom vinterniveauet var signifikant højere end sommerniveauet (5). Sygehistorierne, der er beskrevet af Arbejdstilsynets læger i forbindelse med virksomhedsbesøg, illustrerer et betydeligt kendskab til opløsningsmidlernes toksiske virkninger. Forgiftningssymptomerne er dog også beskrevet i lærebøger fra dette tidlige tidspunkt. Således skriver *Bonnevie* i sin lærebog i hygiejne fra 1951: »Ved den svingende kroniske forgiftning med »tri« ses ofte psykologiske symptomer med stemmnings- og karakterændringer« (12).

Med den mangelfulde datakvalitet i denne undersøgelse kan der ikke drages håndfaste slutninger om generelt eksponeringsniveau vedrørende triklorætylen i den beskrevne 40-års periode. Dette er dog bortset fra anamnestiske oplysninger de bedste historiske danske eksponeringsdata, der findes – langt bedre end de findes tilgængelige for andre organiske opløsningsmidler. De 2.272 biologiske måleværdier i hele perioden analyseret med samme målemetode kan dog formentlig tages som et rimeligt validt udtryk for et udtalt fald i eksponeringsniveauet gennem disse 40 år. I 1940'erne og 1950'erne deltog relativt mange virksomheder i disse biologiske kontrolmålinger på en bredere indikation end i de seneste 10 år, hvor det i højere grad skønnes at være problemidentifikation fra Arbejdstilsynet, der har været den igangsættende faktor. Den reelle forskel i koncentrationsniveauet mellem de 2 ender af tidsperioden kan således meget vel være større, end dette materiale antyder. I henseende til kroniske helbredseffekter, herunder kronisk cerebralt opløsningsmiddelsyndrom, er det således formentlig i et vist omfang fortidens synder, der studeres i disse år.

Til gengæld anvendes organiske opløsningsmidler nu langt mere udbredt end i begyndelsen af vores undersøgelsesperiode. En rapport fra Arbejdsmiljøinstituttet viser også, at eksponeringsniveauet i en del brancher fortsat er højt (13). I denne redegørelse kortlægges forbruget af organiske opløsningsmidler i Danmark i 1985. Blandt 664 repræsentativt udvalgte virksomheder oplyses et forbrug på ca. 2.000 kemiske stoffer og produkter, hvoraf 71% indeholder organiske opløsningsmidler i mærkningspligtige koncentrationer (>1%). På baggrund af undersøgelsen anslås det, at 420.000 personer, eller hver anden person inden for fremstillingsvirksomheder, bygge- og anlæg, sundhedssektoren, service og reparation møder organiske opløsningsmidler på deres arbejde.

På 222 virksomheder er der endvidere foretaget målinger af opløsningsmiddeldampe i luften. I det samlede resultat var 50% af måleresultaterne < ¼ af grænseværdien (GV), 25% af målingerne lå mellem ¼ GV og GV, mens 25% af måleresultaterne lå over GV. De arbejdsprocesser, der hyppigst gav anledning til grænseværdioverskridelser, var: glasfiberarbejdere, manuel kemisk rensning og sprøjtemaling.

De klorerede opløsningsmidler er efterhånden ved at blive afløst af emulgerbare tungtflygtige affedtningsmidler. Men substitutionsprocessen går langsomt. Netop de klorerede opløsningsmidler til manuel kemisk rensning gav anledning til de hyppigste og største overskridelser af grænseværdierne i denne kortlægningsundersøgelse fra 1985, overskridelser på 6-10 gange grænseværdien.

Organisk opløsningsmidler er således næppe noget overstået kapitel i den arbejdsmedicinske historieskrivning.

RESUMÉ

Triklorætylen, et organisk opløsningsmiddel fra gruppen klorerede kulbrinter, har igennem det meste af dette århundrede været anvendt til især metalaffedtning, kemisk tøjrensning og som indholdsstof i lim og lak.

Biologisk monitorering af triklorætyleneksponerede arbejdere som løbende helbredsovervågnng har været anvendt på danske arbejdspladser siden 1947, idet metabolitten trikloreddikesyre i urinen giver et billede af den forudgående uges eksponeringsniveau.

I dette arbejde har man foretaget en opgørelse af samtlige i Arbejdstilsynet registrerede målinger af trikloreddikesyre i perioden 1947-1987 for at få et indtryk af den historiske udvikling i eksponeringsniveau. I alt 2.272 biologiske måleværdier fordelt på 330 virksomheder viser en eksponering på omkring samme niveau fra midt i 1950'erne til midt i 1970'erne, dog med en tydeligt faldende udvikling gennem perioden, idet gennemsnitsværdien i den første 5-års periode var 82 mg/l mod 18 mg/l i slutningen af dette forløb på 40 år.

Disse data er suppleret med sygehistorier fra den tidligste del af perioden, beskrevet af Arbejdstilsynets læger.

En tak til *Poul Bonnevie*, København, og *Svend Sabroe*, Socialmedicinsk Institut, Aarhus Universitet, for kommentarer til manuskriptet.

SUMMARY

Jytte Molin Christensen & Kurt Rasmussen: Exposure of Danish workers to trichloroethylene during the period 1947-1987.

Ugeskr Læger 1990; 152: 464-7.

Trichloroethylene, an organic solvent from the group of chlorinated hydrocarbons, has been employed throughout the greater part of this century particularly for de-greasing of metals, dry cleaning and as a content in glue and lacquer.

Biological monitoring of workers exposed to trichloroethylene as current health supervision has been employed in Danish factories since 1947 as the metabolite trichloroacetic acid in the urine provides an indication of the degree of exposure during the preceding week.

In the present investigation, a review was undertaken of all measurements of trichloroacetic acid notified to the Danish Labour Inspection Service during the period 1947-1987 in order to obtain an impression of the historical development in the level of exposure. A total of 2,272 biological measurements distributed among 330 factories, reveal exposure of about the same level from the middle of the fifties to the middle of the seventies but with a distinct fall during the period, as the average value during the first five-year period was 82 mg/l as compared with 18 mg/l at the end of this 40-years period.

These data are supplemented by case-histories from the earliest part of the period described by doctors from the Danish Labour Inspection Service.

Reprints: *Jytte Molin Christensen*, Arbejdsmiljøinstituttet, Lersø Parkallé 105, DK-2100 København Ø.

LITTERATUR

1. Mikkelsen AB, Petersen R, Rasmussen K, Sabroe S. Klorerede opløsningsmidler – et arbejdsmiljøproblem. København: Fremad, 1983.
2. Vesterberg O, Gorczark J, Krasts M. Exposure to trichloroethylene. II. Metabolites in blood and urine. Scand J Work Environ Health 1976; 4: 212-9.
3. Müller G, Spassowski M, Henschler D. Metabolism of trichloroethylene in man. III. Interaction of trichloroethylene and ethanol. Arch Toxicol 1975; 33: 173-89.
4. Müller G, Spassowski M, Henschler D. Metabolism of trichloroethylene in man. II. Pharmacokinetics of metabolites. Arch Toxicol 1974; 32: 283-95.
5. Lindh T, Ulvarson U, Vesterberg O. Trends over several decades in excretion of trichloroacetic acid after occupational exposure to trichloroethylene. Arbetarskyddstyrelsen, Congress Report on Solvents. Stockholm; Arbetarskyddstyrelsen, 1986.
6. Fallentin B, Kristiansen E, Rietz B. Grafiske virksomheder. Arbejdsmiljøinstituttet. Rapport nr. 15. København: Arbejdsmiljøinstituttet, 1984.
7. Fujiwara K. Über eine neue sehr empfindliche Reaktion zum Chloroformnachweis. Setzber Abhandl Naturforsch Ges Rostock 1914; 6: 33-43.
8. Tanaka S, Ikeda M. Determination of trichloroethanol and trichloroacetic acid in the urine. Br J Industr Med 1968; 25: 214-9.
9. Hunold GA. Die Fujiwara-Reaktion und ihre Anwendung zur Bestimmung von Trichloräthylen in der Raumluft und von Trichloressigsäure in Harn. Arch Gewerbepathol Bewerkehyg 1955; 14: 77-90.
10. Soucek B, Frankova E. Bestimmung geringer Mengen von Trichloräthylen und Trichloressigsäure. Pracov Lek 1952; 4: 264.
11. Christensen JM, Rasmussen K, Køppen B. Automatic headspace gas chromatographic method for the simultaneous determination of trichloroethylene and metabolites in blood and serum. J Chromatogr 1988; 442: 217-23.
12. Bonnevie P. Hygiejne. København: Nyt Nordisk Forlag, 1957.
13. Olsen E, Seedorf L, Laursen B. Organiske opløsningsmidler, kortlægning af deres anvendelse og forekomst af dampe. Arbejdsmiljøinstituttet, 1988; Rapport nr. 26. København: Arbejdsmiljøinstituttet, 1988.