Reference document on exposure to metallic mercury and the development of symptoms with emphasis on neurological and neuropsychological diseases or complaints

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Preface

The present report is a result of a task set by the Danish Health and Safety Research Fund by an announcement made in May 2006 for a reference document on the health effects of metallic mercury. Department of Occupational and Environmental Medicine got the contract and the work has been done by the authors.

The reference document has been reviewed by professor Lars Barregard, Department of Occupational and Environmental Medicine, Sahlgrenska University Hospital and Academy, Gothenburg, Sweden and Dr. Andreas Seeber, former affiliated at the Institute for Occupational Physiology at the University of Dortmund, Germany.

A quality review board, professor Svend Sabroe, Institute of Public Health, University of Aarhus, Denmark and professor Staffan Skerfving, Department of Occupational and Environmental Medicine, Lund University Hospital, Sweden has together with the authors and reviewers made comments on the report on a seminar held in Copenhagen October 12. Afterwards corrections and additions have been made and the revised report has been c submitted to the Danish Health and Safety Research Fund.

Odense November, 09, 2007.

Dansk resumé

Dette referencedokument er baseret på en gennemgang af den videnskabelige litteratur om helbredseffekter af udsættelse for metallisk kviksølv. Baggrunden for dokumentet er et ønske fra Arbejdsmiljøforskningsfonden om
"Referencedokumentet skal på baggrund af en, primært epidemiologisk baseret, gennemgang af de væsentligste internationale undersøgelsesresultater på området sammenfatte og vurdere medicinsk viden, som er af særlig relevans til belysning af de eventuelle årsagssammenhænge mellem udsættelse for metallisk kviksølv, herunder særligt påvirkning på lavdosis-niveau igennem længere tid indenfor tandplejeregi, og udvikling af sygdomme/gener, herunder særligt sygdomme/gener af neurologisk og/eller neuropsykologisk karakter."

Opslaget til referencedokumentet indeholdt en række detaljerede spørgsmål om forhold vedrørende eksponering for metallisk kviksølv relateret til tandplejearbejde, eksponering ved forskellige arbejdsprocesser gennem de sidste 50 år, biologiske mål for eksponering, sandsynlige følger af mangeårigt arbejde med kviksølvholdig amalgam, specielt om muligheden for udvikling af symptomer eller egentlig sygdom flere år efter ophør af eksponeringen. Et særligt ønske har været at vurdere betydningen af gravides udsættelse for metallisk kviksølv for forløbet af graviditeten og for barnets sundhed.
Opslaget med de detaljerede spørgsmål kan ses i det vedlagte bilag 1a.

Anledningen er en debat om mulige senfølger af eksponering for kviksølv hos tandklinikassistenter tilbage i tiden med udvikling af gener af neurologisk/neuropsykologisk karakter. Debatten blev udløst af en norsk rapport fra 2005 som beskrev en overhyppighed af en række symptomer hos tandklinikassistenter i sammenligning med en gruppe sygehjælpere.

Referencedokumentet er opdelt i i alt 6 kapitler 1. Indledning med beskrivelse af metallisk kviksølvs generelle optagelse og helbredseffekter samt en kort beskrivelse af amalgam og dens håndtering i tandplejen. 2: Eksponering for kviksølv i tandplejen. 3. Helbredseffekter af kviksølv i tandplejen. 4. Kviksølvs virkning på den neuropsykologiske funktion. 5) Effekten på forplantningsevnen. 6) Konklusioner

Eksponering for kviksølv i tandpleje-erhvervet

Eksponeringen for metallisk kviksølv i tandplejeerhvervet er blevet fulgt i forskellige lande. især i Norge og til en vis grad i Sverige. Der er foretaget en del målinger i 1960erne, men fra ca. 1975 har der i Norge været et omfattende måleprogram af af kviksølv i urin, som anses som det bedste mål for en persons udsættelse. I Danmark er der kun foretaget få og usystematiske målinger.

Det gennemsnitlige niveau af kviksølv i urinen hos ansatte i tandplejen var i perioden frem til 1969 160-320 nmol/l med betragtelige individuelle variationer idet ca. 10% var over 500 nmol/l. Omkring 1980 faldt det norske niveau til omkring 43-50 nmol/l baseret på et stort antal målinger og faldt yderligere til 22 nmol/l i perioden1990-2000. Senere viste britiske og amerikanske undersøgelser samme kviksølvsniveauer eller lavere. Bemærkelsesværdigt viste svenske undersøgelser fra 1970-90 værdier generelt 50% lavere end de norske målinger i samme periode. Den aktuelle biologiske grænseværdi er i de fleste europæiske lande 200 nmol/l, der arbejds med forskellige lavere såkaldte aktionsværdier.

Niveauerne for tandlæger og tandklinikassistenter var på næsten samme niveau, mens den noget mindre gruppe af tandteknikere frem til 1984 havde værdier 100% højere end de to øvrige grupper.

Nogle af forskellene i mængden af kviksølv i urin skyldtes arbejdsmetoder og indretningen af klinikkerne. Mængden af kviksølv i urinen øgedes med antallet af fyldninger med en variation på 27 til 48 nmol/l (80%) mens trægulve øgede mængden med ca. 30% i sammenligning med fliser eller linoleum, mens andre karakteristika af klinikkerne var af mindre vigtighed i disse ældre studier. Der kunne ikke findes systematiske forskelle mellem mænd og kvinder, som ikke skyldtes forskelle i arbejdsfunktionen.

Den umiddelbare eksponering målt som koncentrationen af kviksølv i luften i indåndingszonen kunne give en bedre beskrivelse af kilderne til eksponering ved forskellige arbejdsmetoder i tandpleje-erhvervet. Et antal ældre studier fra 1957 til 1980 fandt, at hovedkilden til inhaleret kviksølv med eksponeringer så højt som 2 mg/m^3, men for det meste omkring 0.15 mg/m^3, var når gamle fyldninger skulle bores ud. Dette var væsentligt højere end i forbindelse med isætning af fyldninger. Anvendelsen af sug nedsatte denne eksponering ved udboring af plomber med en faktor 10-50. den aktuelle grænseværdi i Danmark er 0.025 mg/m^3.

På grund af forureningen omkring tandlægestolen var kviksølvskoncentrationerne i

luften højere end i andre områder i klinikkerne. Dog var koncentrationen i området omkring amalgam blandingsmaskinerne og affaldsbeholderne på samme niveau som omkring tandlægestolene. Ventilation begrænsede koncentrationerne noget, men forskelle i arbejdsmetoderne havde større betydning.

Af de forskellige metoder til fremstilling af amalgam gav manuel blanding, for eksempel i morter anledning til højere værdier end ved brug af lukkede systemer mens brugen af præfabrikerede kapsler nedsatte antallet af høje koncentrationer yderligere. Antallet af rapporterede spild er blevet sammenstillet med koncentrationen af kviksølv i urin, men en direkte årsagssammenhæng er ikke blevet dokumenteret. En direkte effekt er mulig, men spild kan også være en indikator for dårlige hygiejniske tiltag generelt.

Brugen af kobberamalgam har haft særlig bevågenhed. Under opvarmningen af kobber amalgam kunne høje koncentrationer af kviksølv måles i luften i korte perioder, men vendte tilbage til baggrundsniveauet efter få minutter. Der er imidlertid foretaget meget få målinger, og betydningen af kobberamalgam på kviksølvsmængden i urin er ikke rapporteret.

Eksponering for metallisk kviksølv sker hovedsagelig ved indånding. Optagelse af kviksølv gennem huden er kun blevet undersøgt i begrænset grad. Den er sandsynligvis kun få procent af inhalationen og vil vise sig i kviksølvsniveauet i urinen. Den mulige hudoptagelse ved blanding og modellering af amalgam i hænderne må derfor ikke anses som et større skjult problem.

Helbredseffekter af kviksølv i tandpleje-erhvervet

Akut kviksølvsforgiftning er karakteriseret ved neurologiske og neuropsykologiske symptomer og problemet har været i hvilken grad disse effekter kan detekteres som følge af eksponering i lavere niveauer. Der er rapporteret meget få reelle kviksølvsforgiftninger i tandpleje-erhvervet og symptomer på forgiftning har været meget uspecifikke. Derfor er effekterne af eksponering for kviksølv hovedsageligt blevet baseret på at vise mindre forringelser i forskellige neuropsykologiske funktioner, ved sammenligning med ikke-eksponerede personer. En række af disse studier er blevet udført i tandplejeerhvervet, enten ved at se på relationen til mængden af kviksølv i urinen eller ved sammenligning med eksterne kontrol grupper.

Tre større studier er af stor interesse. I en undersøgelse fra Singapore havde tandlæger, som var eksponeret for kviksølv svarende til urinniveauer på omkring 125

nmol/l forringede præstationer i et antal funktioner sammenlignet med kontrolgruppen. Ved opdeling af tandlægerne i en høj- og laveksponeret gruppe med henholdsvis 240 and 75 nmol/l kviksølv i urin, udviste høj-niveau gruppen størst forringelse i den psykologiske præstation. En skotsk undersøgelse af tandlæger med et gennemsnitsniveau på 27 nmol/l gående op til 220 nmol/l viste ingen forringelse i forhold til kontrolgruppen(1).

En omfattende amerikansk undersøgelse af mandlige tandlæger og kvindelige tandklinikassistenter viste meget lave niveauer af kviksølv i urin, i gennemsnit henholdsvis 16.5 nmol/l og 9.9 nmol/l. Den højeste enkelte måling var 100 nmol/l, niveauer, som ligger indenfor normalområdet for amerikanske borgere uden erhvervsmæssig eksponering. Inden for både tandlæger og klinikassistenter blev der fundet sammenhæng mellem kviksølv i urinen og forringet ydeevne i flere neuropsykologiske funktioner. Effekterne kunne hovedsagelig ses ved test af den motoriske koordination, men også i andre funktioner. I disse undersøgelser var forringelsen af ydeevnen relateret til det aktuelle niveau af eksponering, mens varigheden af eksponeringen ikke havde nogen betydning.

Undersøgelserne kan indikere en virkning af aktuelle eksponeringsniveauer under 150 nmol/l og muligvis endnu lavere hos personer i tandpleje-erhvervet. Da det drejer sig om tværsnitsstudier, registreres der kun associationer, mens årsagssammenhænge ikke kan bestemmes. Der kan ikke opnås oplysning om tidsforløbet af eksponering og effekt med disse studier.

Effekten af kviksølv i urinen på den neuropsykologiske ydeevne og symptomer er blevet analyseret i tre omfattende meta-analyser baseret på undersøgelser fra forskellige erhverv inklusiv tandpleje-erhvervet.

Undersøgelserne viser, at den tydeligste effekt af kviksølv ses i test af den motoriske koordination, i mindre grad i test af hukommelse og i endnu mindre grad i opmærksomhed. Tydelige effekter kunne ses efter lang tids eksponering for kviksølv med koncentrationer af kviksølv i urinen på omkring 500 nmol/l mens en koncentration på 100 nmol/l ikke viste nogle sikre effekter. En mindre effekt kan ikke udelukkes da analyse af sammenhængen mellem eksponeringens størrelse op til 500 nmol/l og effekterne ikke tydede på nogen tærskel for virkningen, men kan fortolkes som lineær sammenhæng mellem dosis og effekter. På trods af en betydelig lavere gennemsnitlig eksponering i tandplejeerhvervet var størrelsen af effekterne sammenlignelige med undersøgelser fra andre erhverv. Der var ingen sammenhæng mellem varigheden af eksponeringen og effekten på symptomer eller præstationen i

de neuropsykologiske test.

I undersøgelser hvor eksponeringen for kviksølv var ophørt, var effekterne mindre og blev mindre jo længere tid der var gået siden ophør af eksponeringen. Ingen af studierne viste nogen forværring af symptomer i årene efter ophør af eksponering. Undersøgelser af grupper af personer med tidligere kviksølvsforgiftning viste enten svagere eller uændrede symptomer efter ophør af eksponering, men ikke nogen tegn på forværring.

Med hensyn til hyppigheden af symptomer som følge af eksponering for metallisk kviksølv har resultaterne været mindre tydelige. I de ovennævnte studier var effekterne af ydeevne tydeligvis mere konsistente end de rapporterede symptomer. Symptomerne har varieret og har ikke vist noget specifikt mønster eller nogen relation til mængden af kviksølv i urin. Der er vist nogle sammenhænge med tidligere og aktuelle eksponeringer vurderet på basis af selvrapporterede oplysninger, men alle rapporterede symptomer er meget almindelige i den generelle befolkning og viden om den potentielle skade i den undersøgte gruppe har helt sikkert været meget vigtig for rapportering af symptomer.

Sygdomme lang tid efter ophør af eksponering

Den igangværende diskussion om tandklinikassistenter med en potentiel eksponering for kviksølv i fortiden kan have udviklet reelle kviksølvsrelaterede sygdomme 20 til 30 år efter den relevante eksponering er blevet baseret på et stigende antal symptomer i en mindre og en større norsk spørgeskema undersøgelse af tandpleje-personale .

Den største af de to spørgeskemaundersøgelser fandt et stigende antal symptomer af både neurologisk og generel karakter hos tandklinikassistenter sammenlignet med en kontrolgruppe, mens tandlægerne havde en væsentligt lavere frekvens af symptomer end kontrolgruppen.

Spørgeskemaundersøgelserne giver et indtryk af problemer hos tandklinikassistenter, men sammenhængen med kviksølv er diskutabel. Tandlægerne havde de samme tidligere urinniveauer af kviksølv som tandklinikassistenterne og der var kun sparsom sammenhæng mellem symptomer og den selvrapporterede eksponering. En større amerikansk undersøgelse og en mindre undersøgelse fra New Zealand fandt heller ikke noget karakteristisk mønster af symptomer. Især var der ikke overhyppighed af motoriske symptomer (dvs. svaghed og mangel på koordination),

som ville kunne forventes ud fra undersøgelserne af neuropsykologisk ydeevne.

Spørgeskemaundersøgelserne er senere blevet suppleret med en mindre undersøgelse fra New Zealand og en supplerende undersøgelse af en undergruppe fra det norske studie. I disse undersøgelser blev der foretaget test af den neuropsykologiske funktion. Ingen af studierne viste nogen tydelig sammenhæng med eksponering. Der blev heller ikke fundet nogen sammenhæng mellem forekomsten af symptomer og den neuropsykologiske funktion.

På basis af resultaterne af undersøgelserne symptomer og den neuropsykologiske funktion kan der ikke findes noget klart mønster for en kviksølvsrelateret neurologisk sygdom hos tandpleje-personalet. Der kan blandt kviksølvudsatte være en lille gruppe med persisterende tegn og symptomer som følger af en tidligere kviksølvsforgiftning. Der kan have været en særlig høj eksponering som sandsynligvis vil have givet tegn på akut kviksølvsforgiftning.

Det kan på den anden side ikke udelukkes, at der på gruppebasis er sket en mindre forringelse af især motorisk koordination på grund af kviksølvseksponering. Dette kan ikke ses hos den enkelte person, men understreger vigtigheden af at holde eksponeringen for kviksølv på et absolut minimum.

Effekter på forplantningsevnen

Undersøgelse af metallisk kviksølvs virkning på forplantningsevnen (reproduktion) hos mennesker er sket ved undersøgelser af evnen til at blive gravid (fekundabilitet), hyppigheden af spontane aborter, for tidligt fødte og for små børn, dødfødsler samt eventuelt medfødte misdannelser. Derimod er der ikke undersøgt om eksponeringen har betydning for børnenes psykomotoriske og sociale udvikling.

I undersøgelserne af de reprotoksiske effekter af metallisk kviksølv hos tandplejepersonale fandtes ikke tegn på ændret fekundabilitet i store, veludførte register studier i Sverige og Norge samt i studier i Danmark, USA og New Zealand. Frekvensen af dødfødsler og lav fødselsvægt var ikke forhøjet hos tandplejepersonale.

Med hensyn til spontane aborter viste et nyligt finsk studie en lettere øget risiko hos de personer som rapporterede en middelhøj eksponering for kviksølv, men ikke hos den højest eksponerede gruppe eller hos tandplejepersonale generelt, når de blev sammenlignet med kontrolgruppen. Registerstudier fra Sverige har ikke vist nogen forøget risiko.

Der kan derfor kun findes enkelte indikatorer på påvirkninger af forplantningsevnen. Disse kan skyldes eksponering for metallisk kviksølv, men også andre stoffer i tandplejen. Da der ikke er blevet publiceret noget dansk register studie kan resultaterne af det igangværende studie måske tilføre vigtig viden.

Opsummering, evidens for årsag

Til vurdering af årssagssammenhænge mellem udsættelse for metallisk kviksølv i tandplejeregi og udvikling af neurologiske eller neuropsykologiske sygdomme eller symptomer skal nøglespørgsmålene i opgavebeskrivelsen for referencedokumentet (see addendum 1 a) hermed besvares:

Der er stærk evidens for, at eksponeringen for metallisk kviksølv i tandplejen frem til 1970 har svaret til en biologisk dosis på gennemsnitligt 125-200 nmol/l med individuelle målinger op til ca. 500 nmol/l. Herefter er de gennemsnitlige urinværdier gradvist faldet til omkring 25 nmol/l med individuelle værdier som sjældent overstiger 100 nmol/l.

Der er stærk evidens for at specifikke procedurer har givet anledning til høje koncentration af kviksølvdampe i luften, mens urinudskillelse af kviksølv kun har været relateret til antallet af udførte fyldninger og enkelte forhold vedrørende klinikkernes indretning. Der er ikke evidens for forskel i urinkviksølv for tandlæger og for klinikassistenter.

Der er stærk evidens for at eksponering for metallisk kviksølv med urinkviksølv på 600 nmol/l målt i gruppeundersøgelser giver forringelse af præstationer i neuropsykologiske test.

Der er moderat evidens for at den neuropsykologiske virkning af eksponering for metallisk kviksølv enten svinder eller er uændret efter ophør af udsættelsen.

Der er begrænset evidens for at eksponering for metallisk kviksølv i tandplejen svarende til urinkviksølv på 150 nmol/l i gruppeundersøgelser betyder let forringelse af præstationen i neuropsykologiske test.

Der er utilstrækkelig evidens for fremkomst af specifikke neurologiske eller neuropsykologiske sygdomme eller symptomer flere år efter ophør af eksponering for kviksølv.

Der er utilstrækkelig evidens for at der kan afgrænses grupper med forøget risiko for

påvirkning af metallisk kviksølv på basis af køn eller genetisk disposition.

Der er utilstrækkelig evidens for negativ påvirkning af forplantningsevnen hos ansatte i tandplejen målt ved fertilitet, ufrivillige aborter, nedsat fødselsvægt, dødfødsler eller medfødte misdannelser hos børnene.

Behov for viden og yderligere forskning

Oplysningerne om eksponering er hovedsagelig blevet baseret på udenlandske undersøgelser, og der kunne ønskes en bedre beskrivelse af eksponering for kviksølv og andre nerveskadende stoffer i den danske tandpleje gennem tiden. Konstruktion af en model, som beregner eksponering ud fra de forskellige arbejdsprocesser i de forskellige tidsperioder kunne forbedre risikoanalysen.

De danske arbejdsmedicinske klinikker har undersøgt et stort antal tandklinikassistenter henvist med mulige forgiftninger. En systematisk beskrivelse af dette materiale med hensyn til repræsentativitet og information om eksponering, symptomer og opståen af sygdomme kan måske tegne et billede af størrelsen og karakteren af problemet.

Resultaterne af det igangværende registerstudie vil levere vigtig information om opståen af sygdomme og reproduktionsudfald hos tandplejepersonale.
For at vurdere det nerveskadende potentiale af metallisk kviksølv vil det være vigtigt at efterprøve de undersøgelser, som viser tegn på en diskret, men signifikant forringelse af den neuropsykologiske funktion ved de meget lave niveauer af kviksølv i urin. Niveauerne svarer til kviksølvkoncentrationer som findes i den almindelige befolkning, og vil derfor have stor sundhedsmæssig betydning.

1 Introduction

In the follow-up of a debate about the possible chronic effects of former mercury exposure in dental assistants started in Denmark December 2005 this reference document was requested by the Danish Ministry of Employment. The debate was raised in the wake of the ongoing Norwegian debate, which was based on findings in a pilot study of symptoms among dental assistants and nurses helpers from Bergen (2).

The detailed description of the requirements for the content of the reference document is shown in Appendix 1.

A crucial point in the discussion, although not explicitly mentioned in the requirements for the report, is the goal of the report. A goal will be to evaluate whether persons with long term exposure to mercury may have developed a specific disease, which can be mainly attributed to mercury exposure or well-known neurological diseases that to some extend may be attributed to mercury.

The other question is whether and at which level of exposure to mercury may give detectable effects (Lowest (Adverse) Effect Level) and whether these have some specificity which may differentiate the condition from other adverse effects or natural variations in symptoms or objective signs.

The first goal will primarily be of interest in cases of compensation for an occupational disease while the latter will be basis for permissible exposure levels, either occupational or covering the general population.

Most literature on mercury has been addressed on finding biological effects of low dose mercury exposure.

To answer these questions we have formed the report in separate chapters. Chapter 1 is a brief introduction about the fate of inorganic mercury, the toxicokinetics and clinical toxicity based on review articles. As stated in the notice only inorganic mercury (metallic mercury and mercury salts) will be included thereby not reviewing the vast literature about organic mercury as methyl mercury.

Chapter 2 summarizes the knowledge about exposure to mercury in dentistry

including both environmental and biological measurements of inorganic mercury in relation to different procedures during the relevant time frame from 1960 to now.

The long-term effects of inorganic mercury are reviewed in different chapters.

Chapter 3 summarizes the literature about neuropsychological effects in dental personnel.

Chapter 4 contains an effort to discuss the dose response relation based on analyses of epidemiological studies of mercury.

Chapter 5 reviews the epidemiological literature about the possible reprotoxicological effects of exposure to mercury or being employed in dentistry.

Chapter 6 summarizes the results of the previous chapters and present conclusions and recommendations.

The main studies reviewed in the different chapters are shown in tables at the end of each chapter.

A series of reviews of the different aspects of the toxicology of mercury has been carried out.,Table 1-3 gives short descriptions of the most recent and important reviews.

1.1 Methods of the review

Due to the complex task with several questions a broad literary search was made. Firstly the recent reviews on mercury toxicity were read and after this two separate search strategies were followed one on health effects in dentists and one on mercury. The latter was narrowed to inorganic mercury of which the vast literature has been on metallic mercury.

Only studies in humans, either epidemiological studies, case studies, or experimental studies were selected.

In an iterative process broad searches were made, primarily on medline but supplied with OSH-ROM (Silver Platter Occupational Safety, and Health –ROM) EMBASE and SCOPHUS articles were selected and read. Articles in references were selected and read, too.

During the project period repetitive searches were made up to August 15, 2007.

A number of the recent papers on the late possible delayed effects in dental personnel have not been published in scientific papers. Therefore an internet search has been made including governmental notes etc. providing information about past exposure.

All articles have been read and evaluated by a standard form according to the specific topic, and the quality. All articles were filed in the program Reference Manager version 11.

1.2 A short description of the uptake, distribution, and excretion of inorganic mercury

For the personnel in dentistry the relevant routes of uptake may either be inhalation of mercury vapours or amalgam dust or dermal contamination and uptake. Gastrointestinal uptake can be considered as inhaled dust typically deposited in the nose and pharynx and subsequently swallowed.

1.2.1 Inhalation

Mercury is mainly taken up by inhalation. Saturated vapour at 24°C contains about 18 mg/m^3 giving possibility for a very high uptake by inhalation.

Entering the lungs the vapours readily diffuse through the alveolar capillary membrane and enters the blood stream. Being an uncharged monatomic gas and therefore highly diffusible and lipid soluble it is well absorbed in the lung and crosses easily cell membranes including the blood-brain and placental barriers.

74 to 80% is retained in the body and distributed with the blood stream. The time to reach a peak value is 9 hr and the amount of mercury in plasma is 4% (95% CI, 3-5%) of the inhaled dose.

The first few hours after exposure, virtually all mercury in the blood is found in the red cells but after about 20 hrs, the red cell levels have fallen and plasma levels have risen such that the ratio of mercury in red cells to plasma is 2:1. Half-lifes in red cells and plasma have similar values of approximately 80 hr.

Seven to 14% of the inhaled mercury is exhaled within a week, while the rest is distributed in the different compartments. The half-life of distribution from the

plasma compartment is approximately 5 hrs while the exhalation through the lungs decrease with a half-life of about 2 days after inhalation of a single dose. On the other hand the decline in plasma levels of mercury consists of at least two components, a short half-life of less than 1 day followed by a longer one of about 10 days (3).

Within time a larger proportion of the body burden is found in the kidneys. In animal experiments it can account for over 50% of the body burden.
Once inside the cell, mercury vapour can undergo oxidation to mercuric mercury (Hg^{2+}) by the catalase-hydrogen peroxide pathway. This occurs most likely in all tissues, as the pathway is ubiquitous. This catalase-mediated oxidation of mercury vapour is inhibited by ethanol.

Inorganic mercury in blood derived from dental amalgam can efficiently be transferred to breast milk. On average the concentration of inorganic mercury in breast milk is 55% of the corresponding concentration in blood.

Inorganic mercury is accumulated in hair only to a small extent if at all. This low level of accumulation, along with the possibility of external contamination from mercury vapour, argues against hair as a suitable indicator medium for inorganic species of mercury.

The whole-body halflife of mercury in humans is about 58 days, range 35-90 days corresponding to an excretion rate of approx. 1% of the body burden per day. Within the body the shortest half-life is in the chest region, about 1.7 days (range 1.2 to 2.1), while half-life in the head region is about 21 days.

Inorganic mercury elimination is mainly by urinary and faecal excretion. At high level steady state exposure, the faecal and urinary routes accounts for about half each of the elimination. At low-level exposure, the relative fractions are uncertain. After short-term exposure, faecal excretion is dominant in the first week, while urinary excretion becomes dominant some time after ceased exposure.

Consequently, the urinary rate of excretion (mol Hg/mol creatinine or µg Hg/g creatinine), or urinary concentration (nmol Hg /L or µg Hg/L), is the most frequently used biological indicator for exposure to mercury vapour.

1.2.2 Gastrointestinal uptake

When ingesting metallic Mercury less than 0.1% of elemental mercury is absorbed

from the gastrointestinal tract, so it has little toxicity when ingested (4).

Dietary intake of inorganic mercury in the general population is approx. 4 µg Hg and estimated daily intake of all forms of mercury is 6.6 µg Hg, where 0.6 µg Hg is from methyl mercury in fish tissue and the remainder from non-fish sources.

1.2.3 Dermal uptake

It has been suggested that metallic mercury can be taken up directly through the skin when amalgam is moulded in the hands. Uptake may be increased by the warming up in the hands thereby increasing the mercury vapour pressure.

The information about dermal uptake of metallic mercury is scarce. A single experimental study of exposure to radioactive labelled mercury vapours has been found (5). The forearms of five male subjects were exposed using a sealed bag excluding the hand and the concentration of mercury was 0.88-2.14 µg/m^3 for 37-43 min. The persons were followed for 60 days. The study showed an uptake rate calculated as 0.1-0.4 µg Hg per m^2 body area per min. per µg/m^3 Hg in the air. This would correspond to 2 % of the respiratory uptake if the whole surface area of a person is exposed. By using a skin stripping technique it was estimated, that only about 50% of the skin uptake is presented as a systemic body burden as the rest is bound in the upper skin layer and shredded. The whole body concentration reached a maximum after about 10 days followed by a slow decline. The concentration measured over the head was 1.7-27% of the total body burden and the concentration followed in parallel with the whole body concentration. Not indicating any increased deposition in the brain. Urinary excretion within the first 10 days and faecal excretion within the first 20 days amounted to 1.13-4.1% and 2.22-4.5% of the total systemic uptake, respectively.

Although the data is scarce dermal uptake may be a minor contribution to the total uptake. However, there is no indication that the kinetics of mercury taken up this way differs from mercury inhaled. Therefore the urinary excretion of mercury, normally measured as concentrations will reflect this route of uptake.

1.3 Biological indices of exposure

As indices of personal exposure or body burden several different matrices have been used in the articles reviewed in the following chapters.

Blood Hg levels reflect the actual level of mercury. The erythrocyte levels id higher at

the start of exposure while at steady state a relatively constant proportion between plasma and blood of 1:2 is seen (6).
Blood level as a biological exposure index is limited due to a relatively short halflife of 5 days thereby only reflecting the most recent exposure.

Urinary excretion of mercury has been the measure,mainly used as biological moniroting index. At steady state the daily urinary excretion is about 1% of the body burden. Measurement of the urinary excretion requires full sampling of all the urine voided during 24 hours and in field conditions sensitive to incomplete sampling. Therefore, as a proximate the urinary excretion divided by the creatinine excretion is often used. This value can be measured in a spot sample and is expressed in µg Hg/g creatinine equal to 0.57 µmol Hg/mol creatinine. The excretion of creatinine is roughly proportional to the muscle mass, in average mmol /kg body weight per day.

The raw concentration of mercury in urine in µg/l equal to 5 nmol/L is very often used. The problem is varying dilution of the urine why correction for density, osmolarity, or more often creatinene has been used. This has in various studies reported here been done by expressing the amount of mercury by mass of creatinine (µg Hg/g creatinine = 0.57 nmol/ mmol creatinine). An empiric conversion factor assuming a concentration of 1 g creatinine/l gives a conversion factor as shown in table 1-1. This may give some imprecisions, which, however, in the these group means will be diminished.
In steady state some empiric conversion factors between blood and urinary mercury (7). This article showed high correlations between the three values, average concentration in breathing zone, end shift blood values, and next morning urinary concentration in urine. The conversion factor between blood and urine could be calculated to 2.80-3.48 (3.2) nmol/mmol creatinine in urine per nmol/l in blood.

Mercury in other matrices as hair (head or pubic) or nails have been used because the values theoretically reflect an exposure over a longer time than blood or urinary values. However as no accumulation is seen in these matrices and there is a considerable risk of contamination these measures are of generally lower value even though some studies have used them.

In order to facilitate the comparison of the exposure in the different articles a conversion table is used (see table 1-2). Some of the factors are empirical in which case an average was used even though this may imply some imprecision in converting the indices of personal exposure or body burden.

Table 1-2 Conversion factors between the different units of measurements for inorganic mercury used in the reviewed articles. The factors show the factors used when converting from the values in the left column to the values in the top row. **Bold** figures are exact factors, while the other are empiric.

	nmol Hg/L (urine)	µg Hg/L (urine)	nmol Hg/mmol creatinine	µg Hg/g creatinine	Nmol/L (blood)
nmol Hg/L (urine)	1	0.2	0.10	0.17	0.03
µg Hg/L (urine)	5.0	1	0.47	0.84	0.15
nmol Hg/mmol creatinine	10.5	2.11	1	1.75	0.31
µg Hg/g creatinine	5.95	1.19	0.57	1	0.18
nmol/L (blood)	33.6	6.8	3.2	5.6	1

The ACGIH (The American Conference of Governmental Industrial Hygienists) uses the ratio of 1 µg Hg/m^3 in air to 1.22 µg Hg/g creatinine (1 nmol Hg/l equals to 0.14 nmol Hg/mmol creatinine in urine to convert air concentrations to urinary excretion rates for long-term exposures. (6) In the present report, however air concentrations and biological concentrations will be handled separately.

1.4 Dental amalgam

Amalgam consists of about 50% metallic mercury in an amalgam with silver or cupper, with small amounts of other metals such as zinc. It was introduced when Auguste Taveau in Paris in 1826 used a "silver paste" made from five French franc pieces mixed with mercury. The silver coins also contained tin and a small amount of cupper, which gave the mixture more plasticity and a quicker setting time. (8)

1.4.1 Procedures for the use of amalgam in dentistry.

Today most dental amalgam is sold as an encapsulated preparation. The powdered metals and elemental mercury are packed into separate compartments, and the physical divider is broken just prior to use.

Silver-mercury fillings contain 50% mercury and a metal alloy consisting of silver (approx. 70%), tin (approx. 25%), cupper (1-6%) and zinc (0-2%). After mixing there may be an excess of mercury in the amalgam, which is removed just prior placement of the amalgam filling.

1.4.2 Mixing of amalgam

Another previously frequently used method to make amalgam was mixing of mercury and metal alloy in a mortar. Excess mercury was squeezed through a cloth, and the amalgam was then often moulded in the palm of the hand to keep it soft.

Some dental clinics had their own production of capsules filled with mercury and metal alloy and subsequent shakened in a mixing device. Excess mercury was also here squeezed through a cloth.

Another method frequently used in the 1970s and 1980s in Norway was mixing of amalgam in a Dentomat or a similar mixing device. Mercury and metal alloy were added in separate chambers in the device and dosed in a semi-closed system. The device dosed the mixture itself, but it was possible to set it on dry or soft amalgam. The soft amalgam was also here in excess of mercury that had to be squeezed out. Filling of the Dentomat or a similar mixing device involved risk of spills.

Prefabricated closed capsules containing mercury and metal alloy were introduced in the 1980s. The mixture was so precise that it was not necessary to squeeze out any excess mercury. (9).

Cupper amalgam, previously used as filling material in decidual teeth, contained approx. 70% mercury and 30% cupper. The cupper amalgam was easier to use than traditional amalgam because it was more flexible to work with and it was considered to have a better anti-bacterial effect that prevented further attack of caries. When cupper amalgam was prepared from tablets, the tablets was heated using a burner to about 225 °C in a little pan until the mixture was fluent. The heated mixture was transferred to a mortar for further processing before the excess mercury was squeezed through a cloth. Most dental clinics stopped using cupper amalgam in the early 1980s.

1.4.3 Condensation of amalgam

Several methods have been used when condensating amalgam either manually or by ultrasound, vibrator (pneumatic, Cavitron, or electro-mallet).

1.4.4 Polishing and removal of amalgam

Cutting, placing, and polishing of amalgam restorations has been done by various methods. Drilling may be air cooled or water cooled. During this various kinds of

suction devices can be used; High-volume evacuator with an evacuating capacity of 150 L/min., Saliva-extractor (SE) with an evacuating capacity of less than 20 L/min. in air, or Mirror-evacuator (ME) which is a combination of a dental mirror and suction device with an evacuating capacity of 40 L/min (10).

1.4.5 Waste removal

During time waste amalgam has been removed and either storaged under water or different kinds of sealed containers.

1.5 Exposure to mercury by amalgam in own teeth

The amalgam fillings liberate mercury which is evaporated into the oral cavity. When mouth-breathing mercury vapour is carried to the lung where it is absorbed and distributed to the tissues. The rate of mercury vapour release is stimulated/determined by; hot liquids and excessive chewing. Excessive chewing may lead to urinary mercury levels in excess of 120 nmol/L.

The number of amalgam surfaces, especially occlusal surfaces determines the release as 10 amalgam surfaces will on the average cause an increase in urine levels of 1 µg Hg/L urine. Urinary concentrations in people with amalgams are typically about 2-4 µg Hg/L. The rate of release in people with amalgam restoration is 2-17 µg Hg/day.

The removal of amalgam fillings first causes a rise in blood plasma levels followed by an exponential decline lasting about 1 year. In the immediate postremoval phase, the peak plasma mercury level may rise to three to four times higher than the pre-treatment level.

An allergic response can occur in the person having amalgam fillings, but it is so rare that a practicing dentist may not see one case in his or her professional lifetime. The allergic response to the placement of amalgam takes the form of ulceration and inflammation of oral tissues in contact with the amalgam. Allergic skin reaction to metallic mercury is very rarely seen.

For a review of the toxicity of dental amalgam in own teeth see Bates 2006 (11).

1.6 Clinical toxicology of inorganic mercury

Acute poisoning with high doses of inorganic mercury appears to occur in three phases: An initial phase with flu-like symptoms lasting 1-3 days. An intermediate phase with signs and symptoms of severe pulmonary toxicity, and a final phase with

gingivo-stomatitis, tremor and erethism (memory loss, emotional lability, depression, insomnia, and shyness) (6;12;13).

The more chronic toxicity is characterized by tremor and psychological disturbances (excessive timidity, diffidence, increasing shyness, loss of self-confidence, anxiety, and a desire to remain unobserved and unobtrusive) as the main features.

Tremor is characteristic, intentional during guided movements (finger-to-nose test) in milder cases, postural in more severe cases (tremor in the extended arm).

Gingivitis, stomatitis, and excessive salivation are seen.

Severe kidney damage sometimes associated with the nephrotic syndrome (rare), characterized by albuminuria and edema.

Table 1-2 shows the different signs in relation to the air concentrations above which they have been documented.

Target organ	Acute toxicity	Chronic toxicity
Kidneys	Proteinuria(> 0.5 mg/m^3 of air)	Severe kidney damage sometimes associated with the nephrotic syndrome (rare), characterized by albuminuria and edema. Changes in urinary NAG may be taken as an early warning sign of potential mercury damage to the kidneys.
Lungs	Dyspnea, paroxysmal cough, chest pain, pulmonary infiltration, bronchial irritation, pneumonitis(> 1 mg/m^3 of air)	
GI tract	Nausea, vomiting, metallic taste, stomatitis, gingivitis, increased salivation(>1 mg/m^3 of air)	Gingivitis, stomatitis, and excessive salivation.
Peripheral nervous system (PNS)	Peripheral neuropathy(> 0.5 mg/m^3 of air)	
Central nervous system (CNS)	Erethism, tremor (> 0.5 mg/m3 of air)	Tremor, intentional in milder cases, which occurs during guided movements (finger-to-nose test). Postural in more severe cases (tremor in the extended arm). Psychological disturbances (excessive timidity, diffidence, increasing shyness, loss of self-confidence, anxiety, and a desire to remain unobserved and unobtrusive)
In general	Chills	

1.7 Permissible exposure levels

During time the occupational exposure levels set by the national board of labour or board of health have decreased. Mainly the Time Weighted Average concentration for 8 hours work has been the standard. The Danish value is 0.025 mg/m^3 and in most European countries the level varies between 0.025 and 0.1 mg/m^3. The European Union has recommended a value of 0.02 mg/m^3.

2 Exposure in dentistry

The exposure assessments in Danish dental clinics and dental personnel, however, are scarce and unsystematic. Two older published studies have been found (14;15) and only a few and not well documented analyses have been made by the Danish National Institute of Occupational Health (16;17).

The tables 2-1, 2-2, and 2-3 describe shortly the results of the various studies showing measurements in air and urine, Detailed information of the measured values in air, urine, blood and other body compartments are shown in appendix 3.

Urinary excretion of mercury has both in dentristry and other exposures been most frequently used due to the easy sampling and because the measurement reflect a relevant time of exposure due to a half time of about 60 days. Some studies have used blood levels of mercury reflecting a shorter exposure period while some studies were based on hair and nail concentrations of mercury theoretically reflecting a long term exposure.

2.1 Mercury in air in relation to the type of clinic and procedures

The most relevant information about air measurement in relation to different circumstances in dental clinics is shown in table 2-1.

2.1.1 Older studies, observations before 1990

Frykholm has in his thesis from 1957 reported measurement of the concentration of mercury in the breathing zone of patient, dentist and dentist´s nurse during preparation and application of amalgam including preparation and insertion of cupper amalgam (18).

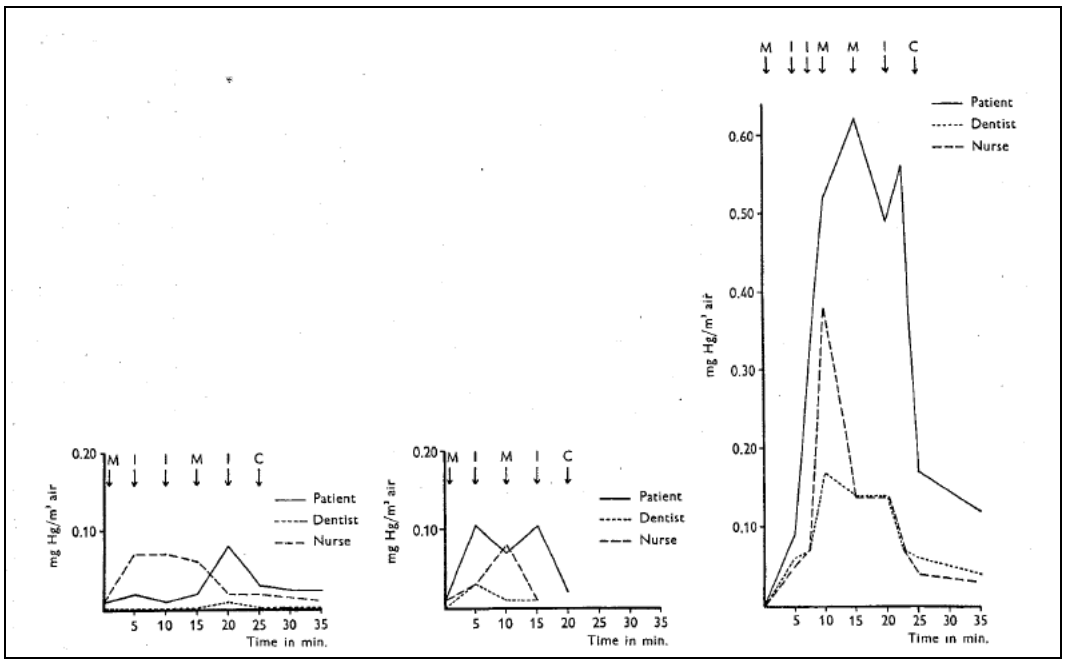

Figure 2-1 Illustration from Frykholm 1957. The air concentrations of mercury in inhaled air of the patient, dentist, and nurse during mixing (M), insertion (I), and completion (C) of silver amalgam (two figures at the left) and cupper amalgam (right) (18).

Concentrations were measured using a directly reading detector(19). The exposure were characterized by peaks in the exposures, up to 0.1 mg/m^3 for traditional amalgam and 0.39 mg/m^3 for cupper amalgam but with very fast decline in concentrations within 5 min after end of the procedures.

Measurements at four different departments at the Royal Swedish School of Dentistry from 1946 to1957 is reported by Frykholm. More than half of the 110 measurements were below 0.01 mg/m^3 while a few ranged up to 0.13 mg/m^3, the laboratory department showing slightly higher values than the operative departments.

A later study by Frykholm investigated Swedish dental personnel (10 dentists, 10 dental nurses, 10 dental technicians) from five workplaces (20). Analysis of air, blood and urine were made. A recommended upper limit of 0.05 mg Hg/m^3 air was not exceeded in the work-places used by dentists and dental nurses. However, during occasional brief periods these limits were reached or exceeded in several dental technical laboratories, e.g., during preparing and polishing amalgam models.

The total mercury and vapour concentrations and the urinary excretion of mercury in 50 dentists were measured in a group of dental offices in New York (21). The means and ranges for vapour mercury concentrations in the operating rooms were 0.020 mg/m^3 (0.002-0.160) and for the waiting rooms 0.018 mg/m^3 (0.002-0.100). The mean total mercury concentration (vapour and particulate) in the operating rooms at a height approximating the breathing zone of the dentist was 0.045 mg/m^3

(0.004-0.410). Fourteen percent of the operating rooms exceeded the actual TLV for mercury of 0.1 mg/m^3. The mean urinary mercury contents of the dentists were 200 (0-775) nmol/L.

The work environment and procedures of 22 Norwegian dentists and their 33 assistants were evaluated by Norseth (22). Determinations were made of the mercury vapour concentrations in the offices, the urinary excretion of mercury and the mercury concentration in blood. The mean mercury vapour concentration of all 24 offices were 0.043 mg/m^3 ranging from 0.00 to 0.400 mg/m^3. In three of the 24 offices surveyed, mercury vapour concentration exceeded the threshold limit value of 0.05 mg/m^3. Especially heating of cupper amalgam, used in children, raised the concentration of mercury vapour in all offices (e.g. from 0.001 to 0.005 mg/m^3 and from 0.01 to 0.08 mg/m^3).

In Denmark Lundgaard 1981 measured the Hg in air at various places (14). The mercury vapour level was measured for 6 days, 3 days with open windows and 3 days with closed windows. By a Dentomat the values were between 0.01 and 0.065 mg/m^3 irrespective of the use of windows. The concentrations were slightly higher when the Dentomat was in use and further increased by a factor 1.5-2 when the lid was not fastened. Residues of amalgam on the work table gave rise to higher concentrations. Comparing the levels of the ventilated and not ventilated rooms, the mercury vapour level was somewhat lower in the ventilated rooms (0.002->0.1 mg/m^3 vs. 0.008->0.1 mg/m^3).

Buchwald surveyed the work environment and procedures associated with the preparation of mercury amalgam fillings of 23 US dentists and their assistants (23). Amalgam dust was measured which cannot be compared with the vapours concentrations. Measuring dust during removal of old fillings the use of suction devices decreased dust values by a factor 14. Water coolant caused lower levels of dust compared with air cooling.

2.1.2 Studies later than 1990

Pohl and Bergman conducted a study in Sweden with the aim to evaluate directly the dentist's exposure to mercury vapour during the cutting, and filling of 50 amalgam restorations and during the polishing of 80 restorations, while using various dental suction devices (10). During the cutting, filling, and polishing operations using a high-volume evacuator, the mean mercury vapour levels in the breathing zone of the dentist were in the range of 0.001-0.002 mg/m^3. However, when only a saliva extractor was used, the cutting of amalgam fillings caused at least a factor 10 higher

and highly fluctuating mercury vapour levels. During condensing and polishing lower values were seen.

During a clinical simulation of insertion and removal of dental amalgams Powell recorded mercury vapour levels (24). The levels increased slightly, but never exceeded the TLV of 0.05 mg/m^3.

The Scottish study by (25)measured in relation to the study of health effects the environmental measurements of mercury in 180 dental clinics (25). One hundred and twenty two (67.8%) of the 180 surgeries visited had environmental mercury measurements in one or more areas above the Occupational Exposure Standard (OES) set by the Health and Safety Executive (0.025 mg/m^3). In the majority of these surgeries the high levels of mercury were found at the skirting and around the base of the dental chair. In 45 surgeries (25%) the personal dosimetry measurement (i.e. in the breathing zone of dental staff) was above the OES.

The use of an amalgam mixer showed higher values than when using prefabricated capsules. The concentration varied considerably between measurements within each procedure while the differences between procedures were smaller. However the highest values were around the chair and these did reflect the dosimeter values of breathing air zones concentrations as well as the biological measurements. The air concentrations at the various sites were correlated with the reported number of amalgams placed.

2.2 Urinary mercury in dental personnel

See table 2-2

In Norway a comprehensive monitoring program has been carried out for urinary mercury in dental personnel. Lenvik et al.(26) have conducted a statistical analysis of data also shown in a recent report (STAMI). Data consists of 6283 samples from 3112 participants for the period 1959-2000. The number of measurements before 1970, however were small compared with the next decades. Main results are shown in table 2-2.

The results show a regular decline in urinary mercury levels in dental personnel from the 1960s and on to 2000. As the table above shows, dental technicians had the highest mean concentration with a median of 340 nmol/l urine in the 1960s and 33 nmol/l urine at the end of the 1980s.

Dentists had a median of 240 nmol/l in the 1960s decreasing to 22 nmol/l in the

1990s. Corresponding values for dental assistants were 160 and 21 nmol/l. Dental hygienists are represented with 17 samples for the period 1975-2000 with a median of 26 nmol/l, which is on the same level as in the general population. These median values cover a considerable variation. For dentists the highest value in the early period was 528 nmol/L and the 10 % highest according the figure was dimished from 500 nmol/L in the 60s to below 100 nmol/l in the 90s.

Up to 1970 64% and 63% of the samples from dental technicians and dentists, respectively, exceeded 200 nmol/l, which in EU has been suggested as biological threshold value for mercury in urine. Corresponding values in dental assistants were 41%. After 1990 no measurements above 200 nmol/L have been registered in any of the groups.

The representativity of the material is, however, not documented in the available literature. In the monitoring program persons with high values have a higher probability for being reexaminated, thereby giving an overrepresentation of the high values. This effect is very often seen in surveys of exposure. A further analysis of this very large material in case better background information could be provided, an analysis of the within person variation would probably give a better description of risk groups.

Battistone (27) determined mercury levels in the urine of 38 dentists and 32 assistants in six different clinics in the US army. Twenty non-dental personnel were used as controls. Mean urinary mercury values, ranging from 15-85 nmol/L and 25-620 nmol/L, were obtained for the controls and dental personnel, respectively. The six clinics included were of two basic designs. Two clinics consisted of large, rectangular rooms with a number of dental units on both sides of the length of each room. The mean urinary mercury values for these two clinics were 280 and 180 nmol/L, respectively. The rest of the clinics consisted of rows of adjoining operatories, a central corridor, and rooms opposite the operatories devoted to supply, administration, etc. The mean urinary mercury values for these clinics were 110, 105, 130 and 65 nmol/L, respectively. This shows that with regard to mercury hygiene, the single-large-room design is less desirable than individual dental units located in separate but adjoining rooms.

Schneider (28) conducted an environmental health survey of 19 US dental offices with 284 dental workers to determine sources of uncontrolled exposure to mercury vapour. An additional objective was to assess the degree of risk of the various dental groups, in the handling of mercury. Dental assistants who handle mercury and

amalgam had higher mean urinary mercury levels than dental assistants whose duties did not include the handling of amalgam (188 vs. 84 nmol/L, respectively), significant $p < 0.01$. The corresponding concentration of the dentists was 123.5 nmol/L for those handling mercury versus 96.5 nmol/L for dentists not handling mercury, not significant. No significant differences were found between dentists who handle mercury and dental assistants who also handle amalgams.

Brooks (29) compared 25 dentists' surgeries in New Zealand with a control group of 20 persons with regards to urinary mercury levels and mercury in hair. Median-values for mercury in the urine samples were for the dentists 87.5 nmol/L (20-316), for the chairside assistants 130 nmol/L (0-1090) and for the control group 17.5 nmol/L (0-178.5).

In the older Norwegian study urinary mercury contents of one dentist and four dental assistants exceeded 250 nmol/L. The mean urinary mercury concentrations in all 22 dentists were 80 nmol/L and in the 33 dental assistants 140 nmol/L (22)

Kelman (30) reports the results of a survey of urinary mercury excretion in 62 Area Health Authority (AHA) and 49 National Health Service (NHS) dentists and dental surgery assistants (DSAs) in Leicestershire, UK. AHA personnel comprised 28 dentists and 34 DSAs; NHS personnel consisted of 21 dentists and 28 DSAs. In both groups of workers the DSAs had a higher mean and greater range of urinary mercury concentrations than the dentists; the NHS workers had similarly, in both dentists and DSAs, a higher mean and greater range of concentrations. Urinary mercury concentrations in AHA; 76.9 (25-115) and 97.5 (25-455) nmol/L for dentists and DSAs, respectively and in NHS; 110.7 (25-500) and 191.3 (25-940) nmol/L for dentists and DSAs, respectively.

In The Netherlands Herber conducted a study of 162 dentists' (all men) and their assistants' (all women) mercury levels in hair and urine (31)30). A threshold level of 0.5 g creatinine/L allowed the determination of 160 urines from the dentists and 152 from the assistants. The mercury concentrations in urine (Hg-U) were somewhat higher in the dentists than the assistants (nmol/L, respectively, vs. 52 nmol/L.)). The method of condensation of amalgam, the number of amalgam fillings per year and hours in own practice were positively related to Hg-U.

A Norwegian study conducted by Jokstad assessed the relationship between mercury exposure and the urinary mercury excretion (32). Morning urine samples and questionnaires were collected from 672 participants in 1986 and 273 participants in

1987. The mean values of the urinary mercury excretion were 39 nmol/L (SD=29) in 1986, and 43 nmol/L (SD=36) in 1987. The mean mercury value was lower for the female (40 nmol/L) than for the male participants (44 nmol/L), ($p< 0.05$). Elevated mercury values correlated with the number of placed, polished, and replaced amalgam restorations/week. Furthermore, participants working in clinics with wooden floors had significantly higher mean mercury values than other dental personnel.

Skare (33) studied mercury exposure among dental personnel in Stockholm, with the use of urinary mercury excretion rates and questionnaires. The study covered 314 dentists (n= 154; 76 men, 78 women) and dental nurses (n= 160, all women). Male dentists had a higher mean concentration, 18 (3.5-80) nmol/L, than their female colleagues, 14 (1.5-55) nmol/L. Dental nurses had a mean concentration of 18 (1.5-75) nmol/L compared to dentists with a mean concentration of 16 (1.5-80) nmol/L. Dental nurses and dentists employed in private practice had a higher mean concentration than their colleagues in public clinics. The reported mean of the mercury concentration in the urine samples of the dentists was 19 nmol/L for private practices versus 11.5 nmol/L for public clinics, and the corresponding concentration of the dental nurses was 20.5 nmol/L for private practices versus 15 nmol/L for public clinics.

In Sweden Akesson (34) investigated Hg-levels in whole blood (B-Hg), plasma (P-Hg), and urine (U-Hg), in various groups of dental personnel (dentists, nurses, dental hygienists) and 81 matched referents, with no known occupational exposure to Hg. The study group consisted of 244 dental personnel in the public dental service, 83 dentists, 153 nurses, and 8 dental hygienists. U-Hg and P-Hg levels were higher in the dental personnel than in the matched referents (U-Hg 18.9 and 11.55 nmol/L urine, respectively; $p< .001$; P-Hg: 6.7 and 6.2 nmol/L, respectively; $p= .03$). Higher U-Hg levels were found in nurses than in dentists (22.05 and 15.75 nmol/L urine, respectively; $p= .02$). No statistically significant differences were observed for P-Hg and B-Hg. Levels of P-Hg and B-Hg were significantly higher in individuals who worked in large clinics than in individuals who were employed at smaller facilities. The oral amalgam status of the dental personnel was determined and statistically significant associations were found between the amount of amalgam in own teeth and U-Hg, P-Hg, and B-Hg ($p< .0001$ for all), with the highest correlation seen between the total amalgam surface area and U-Hg.

Martin (35) examined personal (diet, age and non-occupational mercury exposures), professional (number of amalgams placed per week, whether the dentist uses squeeze

cloths and how amalgam scrap was stored) and office (prior accidential mercury spills, flooring material and number of operatories) characteristics of American dentists to determine which factors contribute most to exposure. Complete data sets were obtained from 1277 dentists, 92.3% male. General dentists constituted 92.4 percent of the study sample. The mean mercury concentration for all subjects was 24.7 (SD=33.05) nmol/L. General dentists had a greater mean concentration, 25.45 (SD=34.1) nmol/L than specialists, 15.8 (SD=11) nmol/L. Men had a higher mean concentration, 24.95 (SD=33.45) nmol/L, than women, 20.6 (SD=24.2) nmol/L. This could be explained by the women having been in their current offices less time, having been in practice less time and having reported fewer accidental spills. Mercury concentration increased with age, from a mean of 19.4 (SD=21.25) nmol/L for those 20 to 30 years of age, to 51.9 (SD=94.25) nmol/L for those older than 70 years of age. Mercury concentration increased with length of practice, from a mean of 24.15 (SD=32.8) nmol/L for the group that had practiced less than five years to 39.7 (SD=70.2) nmol/L for those who had practiced more than 40 years. Urinary mercury concentration increased with numbers of amalgams in the dentist's own mouth, from a mean of 20.55 nmol/L for dentists with no amalgams to 33 for dentists with more than 12 amalgams.

In Israel Steinberg (36) compared urinary mercury levels of 25 dental personnel with 22 controls, not exposed to mercury in their daily occupations, and explored possible correlations between environmental factors in the dental office and the urinary level of the personnel. The results indicated that the urinary mercury levels of the tested dental professionals were significantly higher than those of the control group (14.22 $^{+}$/- 1.9 vs. 5.35 $^{+}$/- 2.023 nmol mercury/L urine). Of the 25 dental personnel and 22 control subjects tested, 18 of the dental personnel (72%) had detectable mercury levels in their urine compared to only 6 (27%) of the control subjects. None of the participants had mercury levels exceeding 150 nmol Hg/L urine. No significant correlation was found between the amount of mercury and years in the profession, weekly working hours, amalgam restorations performed per week, age of the dental office or size of the room. A weak correlation of r = 0.263 was found between the amount of urinary mercury levels and number of amalgam restorations in the mouths of the dental personnel.

Ritchie (25) conducted a study of 180 dentists in the West of Scotland to determine their exposure to mercury during the course of their work and the effects on their health and cognitive function and compared it to 180 controls. Data were obtained from questionnaires distributed to dentists and measurements of environmental mercury in surgeries. Furthermore the dentists were asked to give samples of urine,

hair and nails for mercury analysis. Dentists were found to have, on average, urinary mercury levels over 4 times that of control subjects (27.09 and 7.04 nmol Hg/L urine, respectively) although all but one dentist had urinary mercury below the Health and Safety Executive health guidance value of 20 μmol $mmol^{-1}$ creatinine (~ 200 nmol/L).

In a study by Karahalil (37) the urinary Hg excretion levels of 20 Turkish dentists and nine control subjects, matched for age. The levels of Hg in the urine samples of the dentists was about three times higher than the control subjects (31 +/- 17.5 and 9.85 +/- 4.5 nmol/L, respectively). Some 90% of the dentists wore both gloves and masks. Only one subject wore neither mask nor gloves. Coincidentally, his urinary Hg level was the second highest among exposed subjects. The length of the work experience of the dentists did influence the urinary Hg excretion. Dentists who had been working less than 10 years had a mean urinary Hg level of 25.0 nmo.l/L (SD 12.5)compared to dentists with 10 or more years of work experience 44.5 nmol/L (SD21.5).

2.3 Hg in Blood

In Denmark Moller-Madsen (15) analyzed blood samples from a group of 130 dentists and a control group of 40 blood-donors to evaluate the extent of mercury exposure. The median blood concentration of mercury was 20.0 (range: 6.0-96) nmol/L for dentists and 10.0 (5.5-23) nmol/L for controls. These values are according to Table 1-1 roughly equivalent with urinary concentrations of 100 nmol/L and 50 nmol/L for dentist and controls, respectively.

No statistically significant differences were observed between dentists with different practice characteristics (address of office, private practice/school dentist, number of amalgam restorations performed per week, days since last filling, method of trituration). A statistically significant 47% increase in blood mercury was seen among the examined dentist concerning fish consumption.

Chang (38) collected blood samples from 205 dentists participating in the 1985 Health Assessment Program of the American Dental Association Annual Session. Control blood samples were obtained from the non-dental employees of the Association. The total, inorganic, and organic mercury contents of blood were determined. The results indicated that the total and inorganic mercury levels in blood were significantly different between dentists (30.5 and 10.5 nmol/L, respectively) and nondental controls (20.0 and 3.5 nmol/L, respectively). The organomercurial levels were, however, insignificant. This implies therefore, that

significant enzymatic conversion of inorganic to organic mercury compounds does not occur in vivo.

Atesagaoglu (39) compared blood mercury levels of 10 Turkish dentists with 10 amalgam-free controls. The mean mercury concentration in the blood was 178.5 nmol/L for dentists and 260.5 nmol/L for the controls and showed non-significant differences. The values of this study are a factor 5 higher than in the two above mentioned studies.

2.4 Hg in hair and nails

A number of studies have used hair or nail mercury as biomarkers of exposure (40-42)

Ritchie et al 2004 included mercury in hair (scalp and pubic) and nails in addition to the urinary measurements (1;25). The concentrations were elevated in dentists in comparison with control but the hair and nail measurements did not give additional information about the exposure.

2.5 Gender difference in the biological measurements

Table 2-3 shows the biological exposure indices for males and females in the studies, where this information could be retrieved. Generally the values were 10-20% lower for females although urinary concentrations in two of the Swedish studies show the opposite trend (33;43).

In the Norwegian survey female dentists in all periods, except for the few measurements before 1970 had substantially lower urinary mercury concentrations than their male colleagues, while no systematic difference was seen in dental technicians (44). The female dental assistants had in the first periods higher values than the other groups, probably because of differences in exposure and not gender specific toxicokinetics.

2.6 Discussion and conclusion

2.6.1 Mercury in workroom air.

From the studies it is seen that the exposure in the older studies were higher and more variable up to 1980. After this time the general concentrations in the workroom air were considerably lower although still at least in Brittish dental clinics contaminated with air concentrations exceeding the occupational limits in several places (25). Studies from Scandinavia, other European countries, or from US

showed conditions and exposures that did not vary considerably between countries.

Among the normal procedures conducted with the patient cutting (drilling) old fillings gave the highest exposure to Hg in the dentist's breathing zone which was considerably decreased by a factor five when using a high volume air evacuator or a mirror evacuator (10). A single study indicates that air cooled drills give rise to higher exposure levels than water cooled.

The procedures of mixing amalgam have a considerable impact on the air levels in direct vicinity to the workplace. The older procedures evolving manual handling of pure mercury gave rise to higher levels exceeding 0.05 mg/m^3. The use of mechanical devices (Dentomat and trituator) gave less exposure, but still both direct exposures by handling the fillings and indirectly in the air around the machines depending of the enclosure.

Cupper amalgam has been mentioned several times as giving high exposures and by the description of the procedures heating the product to close to the boiling point of mercury suggest a considerable evaporation. However, in the general literature few measurements could be found and the real influence of this procedure on the total exposure to mercury in dentistry is not documented.

The time spent with each procedure for the various groups of employees in the dental clinics have not been reported why a calculation of a typical time weighted average for a working day can not be made.

2.6.2 Mercury in urine

Urinary mercury has been the mostly used measure of personal exposure. Due to the easy sampling procedure, quality of the analyses, and toxicokinetics, which cause the value to reflect the exposure within the latest months, it has been very frequently used. On group basis the urinary mercury therefore is a well established biological exposure index.

Table 2-2 gives a time trend of the urinary concentrations of mercury . The Norwegian monitoring program shows a steady decrease in urinary content. In the period from 1985 to 2000 it seems that the Swedish studies show considerably lower concentrations than the Norwegian. The studies from other countries during the same period show very similar levels when comparing within each decennium.

Due to the scarce number of Danish measurements it is uncertain whether the

exposure in Denmark in the past period follow Norway or Sweden.

The picture is that the average values in the 60s were about 200 nmol/L with considerable, partly unexplained variations. In the early time the exposure of the dental assistants exceeded those of the dentists'.

Urinary mercury correlated with the intensity of the work calculated as number of fillings etc. On the other hand only scarce information about the type of mixing amalgam is present while a couple of studies have looked at the size and planning of the clinics, work in specific areas of the clinic and especially floor material, where wood floor with cracks give possibilities for spills to evaporate continuously. This seems to have some effects.

Hygienic measures play a large role and changes in work processes using closed systems for preparing amalgam and better waste handling is the primary reason for the large decline in urinary mercury through the three decades. The latest study by Ritchie et al demonstrate that there still is a correlation between mercury in air and urinary mercury even the levels were in the vicinity of 25 nmol/L (25).

Mercury in blood, hair and nails follow urinary mercury in these types of surveys. Despite some theoretical differences they don't add any substantial information.

2.7 Tables for chapter 2

Table 2-1 Air levels of mercury in relation to different technologies/locations in dentistry.

Author, year	Type of technology, flooring, suction, location, etc.	Mercury vapour, (mg/m^3), median-values	No. of measurements)
Joselow(21), USA	Operating rooms; Waiting rooms; Operating rooms;	0.020 (0.002-0.160)[a,e] 0.018 (0.002-0.100)[a,e] 0.045 (0.004-0.410)[a,d]	(50) (50) (50)
Frykholm (19), Sweden Preparation and insertion of fillings. Direct reading meter over 25 min.	Normal amalgam, well ventilated room. Patient; Dentist; Nurse; Normal amalgam, surplus of mercury. Patient; Dentist; Nurse; Cupper amalgam, small room. Patient; Dentist; Nurse;	 0.01-0.09 0.00-0.01 0.01-0.08 0.01-0.11 0.00-0.03 0.01-0.09 0.09-0.62 0.05-0.17 0.05-0.39	
Frykholm (20), Sweden	Treatment room; Sterilization room; Laboratory;	0.01-0.02 (0.01-0.04)[a] 0.015 (0.01-0.03)[a] 0.02-0.14 (0.01-0.49)[a]	(14) (6) (24)

Buchwald (23), USA 1968	Breathing zone of dentist before drilling; Breathing zone of dentist during removal of old amalgam; Near assistant, when old amalgam is being removed; At dentist position, 2-5 minutes after removal of old amalgam; Near assistant, 2-5 minutes after removal of old amalgam; During condensation of new fillings; Operatory; Storage room; Near triturator;	0 0.65[a,d] 0.08[a,d] 0.02[a,d] 0.03[a,d] 0.032 (0.008-0.050) 0.029 (N.D.-0.090) 0.025 (0.005-0.080) 0.028 (0.005-0.053)	(1) (1) (1) (1) (1) (12) (11) (17) (13)
Norseth (22), Norway 1973	Floor, working table, sink, dentist's breathing zone;	0.043 (0-0.400)[a]	Dental clinics (96)
Lundgaard (14), Denmark	Closed windows in the dental clinic. Cleared working table; Working table with remnants of amalgam; By the Dentomat, not in use; By the Dentomat, in use; By the Dentomat, in use, but with loose cover;	0.015-0.030 0.045->0.1 0.008-0.030 0.022-0.035 0.031-0.058	Dental assistants (4) (4) (4) (4) (4)
Chopp (45), 1979-1981, USA, 592 dental offices surveyed. Breathing level in the operatory room Concentrations of mercury vapour greater than the TLV (0.05 mg/m^3);	Capsules of premeasured amalgam; Bulk mercury; Mercury in bulk with open amalgamators; Closed system amalgamators; Open system amalgamators; Did not squeeze excess mercury from the amalgam; Squeezed excess mercury from the amalgam;	0.6% (1) 9% (39) 11% (40) 0% (0) 8% (42) 3.5% (15) 16% (26)	(157) (435) (366) (69) (523) (427) (165)

Nilsson (46)1986, Sweden	Public dental care. Dental chair; Amalgam preparation area; Amalgam scrap container; Private dental care. Dental chair; Amalgam preparation area; Amalgam scrap container;	 0.0016 (<0.001-0.0042)[b] 0.0014 (<0.001-0.0060)[b] 0.0014 (<0.001-0.0060)[b] 0.0028 (<0.001-0.0242)[b] 0.0031 (<0.001-0.0187)[b] 0.0036 (<0.001-0.0194)[b]	In height of breathing zone. (109) (109) (107) (59) (54) (54)
Powell (24), USA	Dispersed-phase amalgam. insertion (15 min.); removal (15 min.);	Dentist's breathing zone 0.014 0.009	(5) (5)
Pohl (10), Sweden	 Cutting, saliva extractor (SE); Cutting + filling, SE; Cutting + filling, high-volume evacuator (HVE) + mirror-evacuator (ME) + SE; Polishing, SE; Polishing, HVE + ME + SE; Condensing, SE;	Dentist's breathing zone 0.168 (0.056-0.442)[a,b] 0.0066[a,b] 0.0015[a,b] 0.0011[a,b] 0.001[a,b] 0.0022 (0.0004-0.0096)[a,b]	(11) (10) (20) (20) (20) (15)
Ritchie (25), Scotland 2001	Dosimeter worn close to the breathing zone; Room air;	 0.0150 (0-0.452)[b] 0.0057 (0.001-0.024)[b]	 (153) (112)

[b]μg/m^3 converted into mg/m^3

[c]airborne particulate mercury

[d]total mercury (vapour and particulate)

[e]mercury vapour

N.D. None detected

Table 2-2 The urinary concentration of mercury in dental personnel in the period 1959-2000. The values are median concentrations, in brackets the lowest and the highest single value and in square brackets the number of measurements.

Period	Reference, country, year	Dentists	Dental assistants	Dental technicians	Dental hygienists
		nmol Hg/L	nmol Hg/L	nmol Hg/L	nmol Hg/L
2001-2005	(37), Turkey 2004	23.5 (8.25-44.05) [14]			
	(25), Scotland 2001	17.85 (0.21-219)[a] [162]			
1990-2000	(26), Norway	22 (6.0-76) [33]	21 (5.0-133) [75]	6.0 [1]	10 [1]
	(35), USA 1991	25.45 (SD 34.1)[b] [1,115]			
	(36), Israel	14.22 +/-1.90SD[b,c] [25]			
	(34), Sweden	15.75[b,d] [83]	22.05[b,d] [153]		17.85[b,d] [8]
1985-1989	(26), Norway	29 (1.5-237) [188]	30 (2.0-319) [434]	33 (5.0-65) [5]	
	(32), Norway 1986-1990	44[b] [864]	69[b] [18]		34[b] [34]
	(43), Sweden	15.8 (<2.1-64.2)[a] [127]	20.0 (<2.1-212.6)[a] [149]		
	(33), Sweden	16 (1.5-80.0)[b] [154]	18 (1.5-75.0)[b] [160]		
	(31), The Netherlands	62 (35.5-111.5)[e] [152]	52 (25.5-106.5)[e] [160]		
1980-1984	(26), Norway	43 (3.3-350) [426]	43 (3.3-365) [1,113]	109 (11-580) [190]	50 (18-210) [10]
1975-1979	(26), Norway	50 (0.0-415) [571]	55 (0.0-1,070) [1,560]	92 (8.5-1,040) [257]	24 (10-180) [6]
	(30), UK	76.9 (25-115)[b] [28]	97.5 (25-455)[b] [34]		
1970-1974	(26), Norway	70 (0.0-760) [286]	80 (0.0-2,400) [643]	121 (0.0-1,650) [162]	
	(22), Norway 1973	80[b] [22]	140[b] [33]		
	(29), New Zealand	87.5 (20.0-316) [26]	130 (0-1,090) [26]		
	(28), USA	123.5 (10-550)[b] [75]	188 (10-1,500)[b] [74]		
	(27), USA	164[b] [38]	164.5[b] [32]		
1959-1969	(26), Norway	240 (83-528) [41]	160 (7.5-3,100) [107]	340 (0.0-1,030) [81]	
	(20), Sweden	25[b,f] [10]	45[b,f] [10]	75[b,f] [10]	
	(21), USA	200 (0-775)[b] [50]			

[a]nmol Hg/mmol creatinine converted into nmol Hg/L
[b]mean-value
[c]μg Hg/g creatinine converted into nmol Hg/L
[d]μmol/mol creatinine converted into nmol Hg/L
[e]geometric mean
[f]mg Hg/L converted into nmol Hg/L

Table 2-3 Measurements in males and females of mercury levels in urine and blood.

Author, year	Gender (Male (M)/ Female (F)) (No. of measurements)	Occupation	B-Hg, median-values (nmol/L)	U-Hg, median-values (nmol/L)
(26), Norway 1959-2000	M (1339) F (206) M (418) F (278)	Dentists Dentists Dental technicians Dental technicians		47 (0.0-760) 40 (0.0-375) 120 (0.0-1650) 101 (5.0-1040)
(41), Lebanon ??	M (89) F (10)	Dentists Dentists		
(35), USA 1991	M (1115) F (93)	Dentists Dentists		24.95 (SD33.45)[a,b] 20.6 (SD24.2)[a,b]
(34), Sweden ??	M (47) F (36)	Dentists Dentists	17.4[b] 16.9[b]	13.65[b,c] 17.85[b,c]
(32), Norway 1986-1987	M (457) F (215)	Dental personnel Dental personnel		44[b] 40[b]
(33), Sweden	M (76) F (78)	Dentists Dentists		18 (3.5-80)[a,b] 14 (1.5-55)[a,b]
(43), Sweden	M (127) F (53)	Dentists Dentists		15.8 (<2.1-64.2)[d] 16.8 (<2.1-48.4)[d]
(15), Denmark 1986	M (77) F (53)	Dentists Dentists	20.5 (6-62)[a] 18.5 (6-96)[a]	

[a]µg/L converted into nmol/L
[b]mean-value [c]µg/g creatinine converted into nmol/L
[d]nmol/mmol creatinine converted into nmol/L

3 Studies of symptoms and neuropsychological performance in dentistry

This chapter contains studies reporting the neuropsychological effects in relation to exposure to mercury in dental personnel. The first part will deal with the recent studies of late effects of past exposure in dental personnel while older studies are reviewed later in this chapter.

The chapter refers to table 3-1 reporting main information of the cited studies.

3.1 Studies of delayed neuropsychological effects in dental personnel

Moen et al made a preliminary investigation of symptoms among dental assistants compared with a group of nurses aides (2). It has been published as a short popular report but not in scientific papers. From a list from the trade union for dental assistants in a county the 94 persons born before 1970 were selected. 87 were contacted and 50 responded. However, only 39 were included in the analyses and they had in average worked 30 years as dental assistants. They were compared with a group of 74 nurses aides recruited in a study of musculoskeletal complaints of who 48 were included in the analyses. The dental assistants were slightly older (59 vs. 54 years in average), and had less general education than the controls.

A questionnaire was filled out including items about neuropsychological complaints from a standard scheme "Euroquest" covering 10 different groups of symptoms.

The dental assistants had higher scores than the controls in all groups of symptoms reaching significance in six groups: Peripheral nerves, confusion, depression, headache, complaints from the gastrointestinal system, complaints from heart and lungs, mood changes, memory, and coordination. After control for age, educational level, smoking habits and consumption of alcohol only depression, memory, coordination, and complaints from heart and lungs reached significance. The latter actually showed the largest difference despite a considerable lower frequency of smokers among the dental assistants. No estimation of the relation to the individual exposure (dose-response) was reported.

The authors conclude that dental assistants had a clearly increased level of symptoms from the central nervous system. The study was small but more research is needed.

The report has had a great impact on the discussion both in Norway and Denmark. The report lacks critical information about the conduction of the study. However, the results may be interpreted as a general higher level of complaints in dental assistants. The difference in heart and lung symptoms was the most pronounced even after correction for differences in smoking habits. Heart and lung symptoms in relation to low dose mercury exposure are not expected.

This report gave rise to a heated political debate in Norway leading to a report about the exposure (44) and a larger investigation of symptoms and neuropsychological performance in dental personnel.

A part of this larger Norwegian study on the symptoms among personnel in dentistry in an area of the middle part of Norway (9)has been published as a report, but not yet as a peer reviewed article. A study of the neuropsychological effects of a subgroup of the dental personnel is under way but will not be finished before the end of 2007 (Hilt, personal communication).

Data for the study was collected in the spring of 2006. Lists over current and former employees in public and private dentistry were obtained from the employers. 2,247 persons born between 1913 and 1985 were identified. A population based control group including 1,500 persons was sampled from the municipal registers. This was selected to get a distribution according to habitation, gender and age comparable with the dentist personnel, but the methods of sampling or matching were not reported.

The persons were sent a set of postal questionnaires. All persons received a questionnaire about neurological and cognitive symptoms, other diseases as well as background factors. The cognitive symptoms were recorded using the Euroquest questionnaire, primarily developed for investigation of the effects of organic solvents.

Besides, a set of questions about reproductive history was included. These included number of children, waiting time to pregnancy, spontaneous abortions, stillbirths, and congenital malformations. The evaluation of the psychological development of the children was operationalized by the need for special teaching or by referral to psychological assistance in school (see chapter 5).

For the dental personnel a questionnaire about exposure included title, time of employment in specific clinics. For each process, handling and heating cupper amalgam, use of a mortar for mixing, filling capsules, using of "Dentomat", and the use of readymade capsules. By multiplication of the reported number of applications of each task per week and weighing the various tasks by the estimated exposure. By this cupper amalgam was given a weight of 100 times the other tasks. Besides a score was made for the number of years where the rooms had been used as a clinic and a weight of 10 was added if larger spillages had been reported and aggravated with a factor 10 if the room had floor mats or tree panels. Additionally, moulding amalgam with the hands was given a score. One or more historical measurements of urinary mercury sampled in routine monitoring were available for about 25% of the persons.

The response rates were 57% for dental assistants, 49% for dentists, and 47% for other employees in dentistry. Among the controls the response rate was 44%. Response rate increased with increasing age.

The median year of start in dentistry was 1974, very few before 1950, about 6% in the period 1950 to 1960. The median cumulated exposure score for assistants, dentists, and others were 216, 137, and 30, respectively, with very skew distributions. On the other hand, the median urinary Hg measurements were much more equal 49, 42, and 49 nmol/l, respectively. The number of handlings of mercury in each category corresponded well between dentists and assistants except for handling cupper amalgam, where the assistants reported twice as many handlings as the dentists.

The average symptom scores of the dentists and assistants were compared separately for each sex with the common reference group. Figure 3.2 shows the values of table 3.3b in the report. Only females are shown as males only were represented among dentists. For comparison the diffences are normalized to z-scores are shown, too.

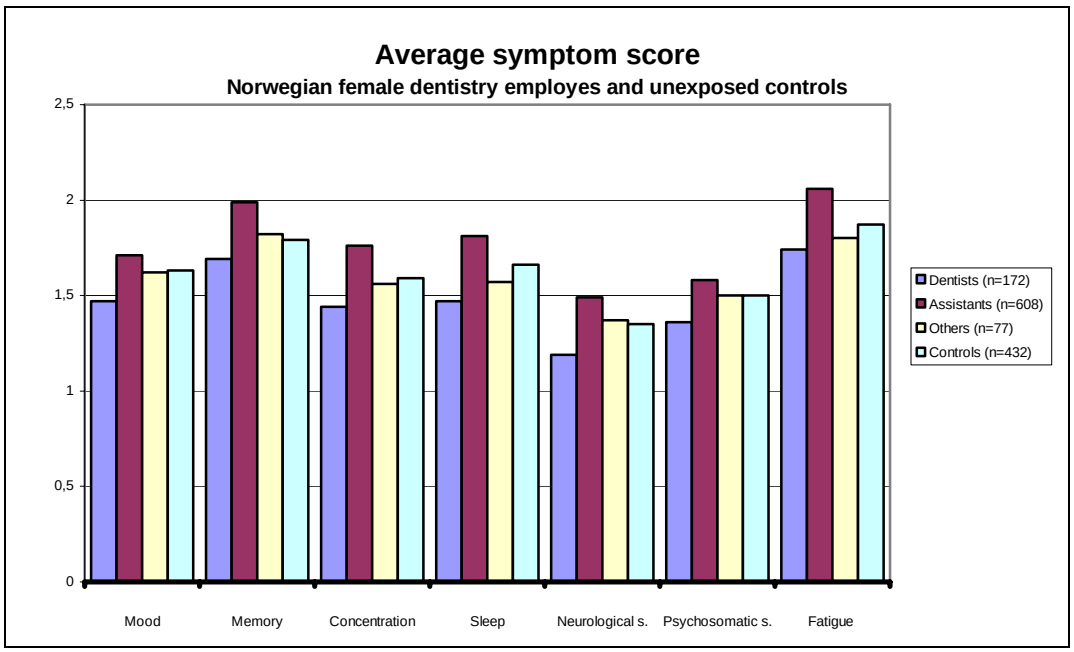

Figure 3-1 The average symptom score in female dental personnel and controls of the seven cognitive symptoms (9) table 3b

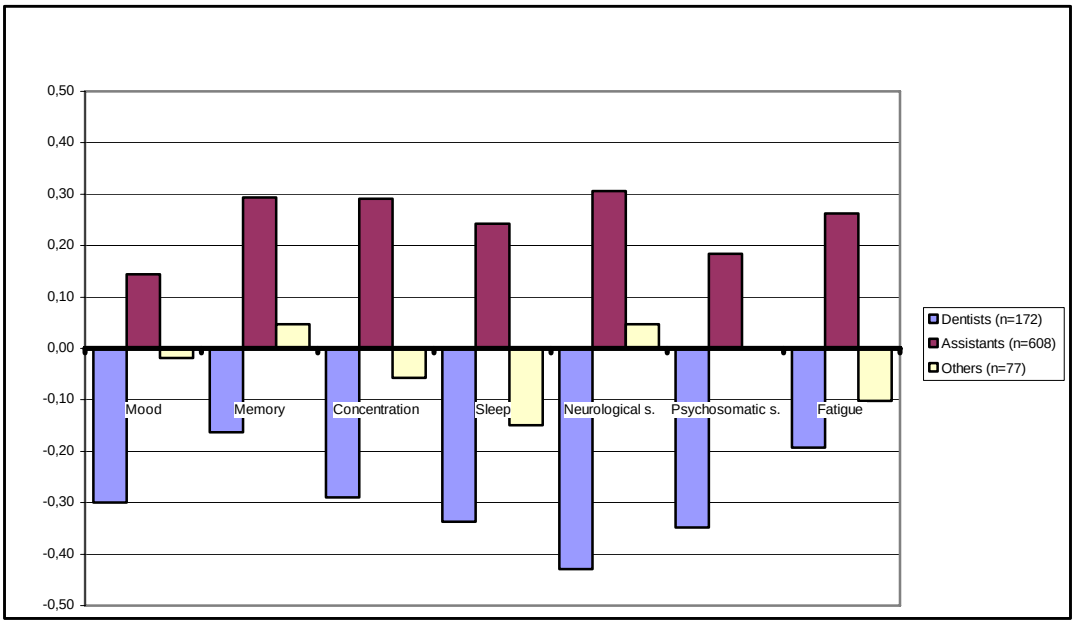

Figure 3-2 Differences between female dental personnel and controls of the seven cognitive symptoms (9). Values are in this figure normalized to z-scores (difference divided by the common weighted standard deviation)

It is seen that there was a considerable difference between the scores of the dentists and the assistants with the other personnel lying in between. The dentists had significantly lower scores than the controls while assistants had higher. Male dentists reported the same levels of symptoms as their female colleagues, and the percentage of persons with the higher scores revealed the same picture. According to other symptoms dentists reported lower frequencies of musculoskeletal symptoms but of longer duration, while no other differences were seen between female dentists and dental assistants.

In the analyses of dose response significant correlations between exposure score and the seven symptoms were shown in the assistants and to some extend in the dentists. However, the range for the lowest to the highest exposure group did not exceed 0.5 steps on a 5 scale. The same relations were seen with questions about different procedures, moulding amalgam in the hand, frequent spillage in the rooms, and the use of cupper amalgam. The differences were between 0 and 0.25, most consistent in assistants, several negative in dentists. When looking at the number of patients with cupper amalgam, a more consistent increase in symptoms with increasing use was seen. In other symptoms and diseases no difference between dental personnel and controls was seen.

The group conclude that there was a dose related increase in cognitive symptoms and that the effect was highest in dental assistants in agreement with a higher both self reported and measured exposure. They recommend that disturbances in cognitive function should be approved and compensated as occupational diseases in Norway (47).

The study is large in comparison with the former studies. The response rate was not high, but acceptable, especially in the older persons, which in this context are the most relevant.

However, the study has several problems. Basically, a comparison was made between a group of dental personnel and a population based control group. The problem is that the dental group was heterogeneous and this large difference between dentists and their assistants will inevitably cause significant differences with a common controls group indicating significant effects in each direction. Another design using either separate control groups matched on social class and education or a matched design would be more appropriate. A more critical analysis with stratification for educational level may give some explanation of the conflicting results for dentists and for the dental assistants.

Besides, the cross sectional design with questions about exposure and symptoms in the same questionnaire is very sensitive to recall bias. This could be suspected in the large difference between dentists and assistants in reporting procedures with potential of exposure and the lack of correlation with the measurements of urinary mercury. The large number of urinary measurements over time may give a possibility for reliable estimates of personal exposure.

The study was done at a time, when the discussion in the Norwegian medias about

the possible dangers of mercury was fresh, and therefore the responses might be influenced by this. The origin of these types of very common symptoms may be due to a neurotoxic exposure but former studies clearly show that the pure knowledge of a potential hazard may give symptoms. Previous attitudes, personal traits, and mental health have influence (48). Although there is no suggestion about any differences in these variables between the dental personnel and the control group, the mere knowledge about potential exposure to mercury supported by a widespread actual debate about the dangers may seriously influence the results. The considerable difference between dentists and dental assistants despite almost equal past exposure based o n the urinary mercury may support this interpretation. However the results of the neuropsychological evaluation of a subgroup of the Norwegian dental personnel may add to the information.

The results of the neuropsychological performance tests of a subgroup of the dental personnel in the study was published in November 2007 just before the deadline of the present report (49)This part included an occupational medical examination, blood tests as well as a set of neuropsychogical performance tests (see table 3.1). From the respondents to the questionnaire study females with low and high self reported exposure scores were selected and 114 were invited to the examination. Of these 91 (80%) were eligible for participation. The set of tests corresponded with those used in other studies (see chapter 4, meta-analyses). The results were expressed as Z-scores in seven domains plus a symptom index.

No relation to exposure expressed as the self reported was seen in any of the domains. In the subgroup with previous urinary mercury tests a significant correlation with visual memory score and a tendency with working memory in the expected direction was seen. There were significant correlations between symptoms in the questionnaires and three of the functional domains, but two of these in the non-expected direction.

Jones et al (50) in New Zealand studied a group of school dental nurses about thirty years after their graduation in 1968-71. This group was chosen, as they had been using cupper amalgam for three years or more. Cupper amalgam was used up till 1975, where it was phased out because a survey of urinary mercury in dental personnel showed high values.

Out of 115 graduates 43 (38%) participated. They were about 52 years of age and compared with 32 age matched controls, either sisters or friends. The exposure of the dental nurses was at least five years of work (two years of training and three years

of bonded employment, while a not reported number had up to 10 years of additional experience (medium exposure) and some more than 10 additional years (high exposure). The persons filled in a questionnaire about general health, reproductive history, and work history. A neurobehavioral test battery was presented as well as testing of "Profile of Mood States".

More dental nurses than controls reported "occupational overuse syndrome" (33% vs. 7%) while no difference was seen in general health. The dental nurses had higher frequencies of seven out of the 33 actual symptoms (arthritis, bloating, dry skin, headaches, metallic taste, sleep disturbances, and unsteadiness). There was no significant difference in any of the five reported scores in the neurobehavioral tests, and the performance in the two groups. In two of the six modalities of the Profile of Mood Score a difference was seen. In the "agreeable-hostile" dimension the nurses were more agreeable and in the "composed-anxious" scale they were more anxious. According to reproductive symptoms only an increased number of hysterectomies in the dental nurses were reported.

Following the Danish debate in 2006 a large number of dental assistants were referred by the general practitioners to one of the 14 regional departments of occupational medicine and examined that year. At these clinics the referred persons were interviewed and examined according to some common guidelines but not a strict protocol. The results have only been reported in a short notice and a report on the internet (51;52). 733 female persons, (729 dental assistants, 2 dentists, and 2 laboratory technicians) with in average 20.8 years work at dental clinics were examined. Main exposure to mercury was in the years up to 1980. Due to normal clinical criteria 11 (1.5%) had symptoms and signs of possible mercury intoxication, all including signs of motor involvement (tremor, ataxia, and dyscoordination). No probable or definite intoxications were reported. 251 (34%) had various chronic diseases in which no relation to mercury was suspected while 269 (37%) reported a various number of unspecific symptoms often occurring several years after the exposure.

The results do not rule out that a large number of long term symptoms and signs are overrepresented in relation to the former mercury exposure. The investigation was not set up as a genuine epidemiological study but the persons were examined according to normal occupational medical practice by a large number of doctors. Therefore the information provided by the interviews and clinical examinations is heterogeneous. However the number of persons investigated was in comparison with most of the studies of mercury very large and clear cases of former acute

intoxications or chronic sequels due to mercury exposure would be found by the trained occupational physicians.

Due to the lack of clear cases of mercury intoxications and only a small number of signs and symptoms suspicious for chronic intoxications this extended case report does not support the presence of a large number of latent chronic intoxications in this group.

No other published studies of dental personnel examined several years after an exposure have been found.

3.2 Neuropsychological measurements in dentistry during exposure

Ritchie et al (1) tested 180 relatively young dentists (mean age 39 years) and 180 somewhat younger university staff members (mean age 32 years). The dentists were primarily recruited by a random sample (72%) but 51 or 28% were self selected. There were more females in the control group than among the dentists (53% vs. 40%). A comprehensive investigation of the exposure revealed relatively low urinary concentrations of mercury, in average 17.85 (0.21-219.45) nmol/L (see chapter 2). Out of eight, mainly neurological symptoms possibly related to mercury, memory disturbance was the only symptom more frequent in dentists, while the other symptoms did not show a trend to either side. For psychomotor performance dentists performed poorer in a vigilance test while in a choice reaction test they were better than the controls. No relation to any of the exposure variables was seen.

The study was large with very detailed individual exposure measurements. The control group was recruited in a population with comparable educational level. However the actual exposure was low and the past exposure less well documented. The results are difficult to interpret as both symptoms and performance were highly correlated with age and partly with sex. Although these variables were included in the analysis this imbalance may have had a systematic effect on the differences.

A Turkish study showed differences in scales of psychological and psychiatric symptoms between dentists and hospital staff despite very low levels of mercury and differences in two variables of a logical memory test, but not in any of the 14 other test scores (53). An analysis of the relation to urinary mercury was done across dentists and controls but this difference could not be separated from the difference between dentists and controls as groups.

A number of older studies have used hair mercury and wrist measurements of mercury (54-56). Both according to measurement of exposure and the statistical treatment there are methodological flaws so the information from these studies is limited.

The two Swedish studies by Langworth et al and Nilsson et al on dentists and dental assistants only reported symptoms in relation to urinary mercury (43;57). The levels of exposure were low and neither any difference between personnel with low and high values of urinary mercury nor between dental personnel and controls were seen in these studies.

Ngim et al in Singapore made comparison of a group of relatively young dentists with controls from university staff (58;59). They showed blood levels about 50 nmol/l (comparable with 125 nmol/L urinary concentration) and found a difference between dentists and controls in a wide range of tests as well as the profile of mood scales. The dentists had a relatively short time of work (7.5 years) but work weeks of 60 hours. In the analyses a correlation between performance and exposure was seen when the dentists were classified as high and low both according to years (GM 125 mths vs. 42 mths.) and blood levels (95 nmol/L vs. 36 nmol/l). The effects were equally seen in all modalities of the neuropsychological function.

Echeverria studied in 1991 dentists attending the annual member conference (60). From 1,706 volunteers providing a urinary sample 29 had values above 95 nmol/L and 19 of these participated as well as 20 out of 150 dentists with non-detectable mercury in urine. Urinary analyses were made at once and the relevant persons participated while attending the conference.

Mean exposure level in the high group was 189 nmol/L. The exposed persons had longer time as dentist, more amalgams placed per week, a considerably higher number used squeeze cloths, and they reported more spills than the non-exposed dentists.

The effects were analysed in relation to urinary values of mercury and porphyrine. A number of symptoms differed between groups and differences were seen in all the mood scales. Differences were seen in two out of seven outcome measures of performance tests, simple reaction time and digit span related to porphyrine level, but not urinary mercury. The study design imply that the urinary levels of mercury is highly confounded with the selection to the group. The shown correlations can therefore not be separated from the differences between groups and the selection of

the participants, especially the controls was not documented.

Bittner et al made a summary of six runs of these investigations of dentists attending the annual conferences (61) only looking on a series of mainly psychomotor test. Again the selection gave rise to a bimodal distribution of urinary mercury with a median in the low group of about 5 nmol/L and in the high group about 150 nmol/L but with some overlap despite the selection process. In this analysis only the test of hand steadiness was related to exposure.

Echeverria and her group have made further studies of major interest. Firstly a limited study of dentists and dental assistants where a chelation challence was used to mobilize mercury in order to get a better estimate of the body burden (62). The urinary levels were low, only ranging to 20 nmol/l. Both pre and post chelation mercury levels correlated with several measures of motor and cognitive tests as well as all the six different modalities of the mood scale. The general symptom score only correlated with the post chelation values.

This study showed an effect at considerably lower values than previous studies. The value of chelation as a measure of body burden may be questioned, as the 24 hour excretion mainly is mobilized from the kidneys (63).

The most recent, larger study included genetic markers of susceptibility in the analysis (64-66). From a survey of American dentists in 1998 they sampled a group of 194 male dentists stratified according to urinary mercury levels. From the clinics of the selected dentists 233 female dental assistants were included, too. The urinary mercury levels at the examination for the dental assistants all lower than 100 nmol/l, thereby considerably lower than in the former studies. The effect of mercury on symptoms and neurobehavioral performance was tested by regression analyses including urinary mercury. No external control group was included. Therefore analyses of a possible individual genetically determined sensitivity to mercury were made Two genetic factors for coproporhyrinogen oxidase, an enzyme in the pathway for the metabolization and excretion of mercury and “brain derived neurotrophic factor” (BDNF), where the polymorphy may be a reflection of variations in memory processes, were investigated.

This study as well as the previous, smaller study with basically the same setup show a remarkable number of significant correlations between the actual urinary mercury and the performance in a vast series of tests. In dentists 10 out of 25 outcomes showed significant impairment with increasing urinary mercury. These were four out

of seven outcomes characterized as manual coordination skills, three out of six outcomes of memory, and three out of eight other tests. In dental assistants with lower urinary mercury 8 outcomes were significant including two tests of manual coordination. A test for multiple comparisons showed that most of the correlations were in the expected direction. A detailed analysis of the test of hand steadiness did not indicate a lower threshold of effect of mercury.

Additionally measures of peripheral nerve conduction velocity was correlated with urinary mercury in dental assistants but the effect was not seen when persons with a history of hand disorders were removed.

The role of the genetic variations in BDNF was as an independent source of variation while the polymorphism did not seem to influence on the susceptibility to mercury. The polymorphism of coproporphyrin oxidase showed some sign of an independent effect while no interaction with mercury was seen, either.

According to a long list of present, recent, and chronic symptoms a remarkable differences were seen (66). Very few correlations were seen in the male dentists and a large number of associations were seen in the female dental assistants. Two out of 11 possible relations between actual symptoms and urinary mercury (anxiety and confusion) were in the expected direction while a large number of symptoms from all organs were correlated with the self reported chronic exposure indices. These indices were not used for the performance tests in the other articles (64;65).

The results showing a dose related impairment in mainly manual skills in both dentists and dental assistants with mercury levels of a size seen in the general population is remarkable. The sizes of the effects could not be calculated directly, but looking at the b-values and the standard errors these lay between 0.1 and 0.3, fairly low values. This is in agreement with relative low significance levels seen for this population size. Due to relative homogeneous study groups the variation is limited thereby increasing the power.

The effects may be genuine and in accordance with the meta analyses (see chapter 4) where motor skills are the most consistent findings. Other explanation may be reverse causation in this cross sectional material as the persons with less motor coordination abilities are prone to a larger contamination from the work. The study, albeit large, still needs to be confirmed in an independent study, preferably in a prospective setting where the direction of causation is clear.

3.3 Discussion and conclusion

The studies of the neuropsychological symptoms and performance in dental personnel present two different problems. One is the recent studies of symptoms in mainly dental assistants or nurses with a past exposure. The others are the cross sectional studies of dental workers with ongoing exposure.

The Norwegian survey has been large with a well defined group of subjects and despite a relatively low participation rate the frequency of symptoms are probably representative for the groups.

The main finding is an increased rate of the general cognitive and emotional symptoms in dental assistants in comparison with control persons. Within the groups a relatively weak correlation with self reported exposure was seen, but the relation to past urinary mercury level was weak. Dentists having worked in the same clinics showed considerably lower frequencies of symptoms and other dental personnel lie in between. However, there was a remarkable likeliness with the study of Heyer showing a vast number of wide spread symptoms from various organs correlating with self reported measures of chronic exposure but not with the actual mercury levels. These relations in cross sectional studies suggest that other than pure toxic mechanisms are present, supported by the difference between the response among dentists and dental assistants in the Norwegian study.

On the other side a series of studies have looked at actually working dentists and controls using neuropsychological performance as outcomes. Some kind of dose response could be derived. In the Singapore study wide spread effects were seen in a group with currently high values of blood mercury corresponding to urinary levels above 125nmol/L (59). Echeverria and Bittner found some, mainly psychomotor effects at average levels of 200 nmol/L (60;61) and length of exposure exceeding 5-10 years.

The two most recent, larger, and methodologically better studies by Ritchie et al and Echeverria et al come to different conclusions of the effect of very low exposures. (1) did not find any significant dose related effects while Echeverria did find dose related impairment in a series of tests.

The type of performance affected at the lowest dose can not be revealed. Psychomotor performance has in the American studies showed the clearest effect, but whether this is genuine or because these tests are easier to reproduce and have the smallest individual variation is not clear.

Therefore, a current urinary level of 100 nmol/l in dentists with several years of practice seem to be the lowest observed level for neuropsychological performance. However, the study of Echeverria may indicate a lower threshold, if any. It is remarkable, that only the actual body burden, mainly expressed as urinary mercury is of importance. The length of exposure did not seem to be of importance, except that the above mentioned difference between the two larger recent studies to some extend may be attributed to a 10 years age difference in the dentists.

The effects on performance after cessation of exposure and normalization of urinary mercury levels in dental personnel have only been investigated in the two small studies (49;50). A marginal relation to previous mercury measurements may be seen in the Norwegian study but nothing can be concluded from the two studies.

The effects, however, in the newer studies are very small variations within normal performances, and only detectable in large homogeneous groups after correction for relevant confounders. Neither in the studies of currently exposed persons or in the formerly exposed any type of case finding of looking for diagnoses. The studies indicate a biological adverse effect of the occupational exposure to mercury, but no specific pattern which could indicate a specific disease.

The role of mercury among other exposures in these studies can not be described. Even that mercury from a toxicological point of view has been the main neurotoxicant dental personnel have been exposed to nitrous oxide as anaestethic gas and minor amounts of solvents.

To investigate the role of occupational exposure to mercury studies in other industries therefore will be discussed in the following chapter.

3.4 Tables for chapter 3

Table 3-1 Neuropsychological and neurophysiological symptoms in dental personnel exposed to mercury.

Author, year, study	Dentistry (no. of measurements)	Exposure	Effects
(50), New Zealand, cross sectional 30-year follow-up	43 ex-School Dental Service employees/ 32 women (sisters or friends of the exposed group) matched for alcohol and tobacco intake and self-reported general health	Mean age in the exposed group was 52.19 yr and 51.39 yr in the control group.	There were no significant differences between the exposed and control groups on the cognitive tests: The Symbol Digit Modalities Test, The Rey 15-item test, The California Verbal Learning Test. The Profile of Mood States (POMS) showed that the exposed group was more agreeable (*P*= 0.04) and more anxious (*P*= 0.03) than the control group.
Hilt et al. 2007 (49) Cross sectional	91 females, 76 dental assistants and 15 dentists. 57 (SD 6.4) years	Two groups: 45 with a low exposure score (<185) and 46 with a high score (>898). In average 18.3 and 30.3 years of practice, 74.8% still in work.	No difference between groups in motoric function (tests), working memory , attention, mental flexibility, visual and verbal memory, tremor or symptom score. A significant correlation between visual memory and previous urinary mercury (26 persons).
(53), Turkey cross-sectional	43 dental personnel (33 dentists, 6 dental nurses, 4 dental technicians) working in teams at five dental clinics/ 43 hospital employees (34 physicians, 5 nurses, 4 health-technicians) not exposed to mercury.	Average duration of exposure was 10 yr. (range 4-27 yr.). Median yr. of age was 32 (range 23-54) for dental personnel and 31 yr. (range 24-50) for controls. Median U-Hg level: Dental personnel 10.2 nmol/L[c] (range 0.1-35.7). Controls 4.2 nmol/L[c] (range 0.1-29.1). Median B-Hg level: Dental personnel 1.81 nmol/L (range 0.07-4.64). Controls 1.20 nmol/L (range 0.10-5.01).	The dental personnel displayed statistically significant lower scores than the controls with respect to Logical Memory. In the SCL-90-R, dental personnel showed significantly higher scores on reported Global Severity Index (GSI), Positive Symptom Total (PST) and Positive Symptom Distress Index (PSDI), Somatisation, Obsessive-compulsive, Anxiety, Hostility, Psychoticism than controls. The dental personnel had significantly increased depression scores according to the Beck Depression Inventory (BDI).

Echeverria, Heyer et al (64-66) US, cross sectional	194 male dentists, 49.0 (SD 7.8)y and 233 female dental assistants 36.0 (SD 9.1) y	16.5 (SD 24.4) nmol/l for the dentists and 9.9 (SD 11.45) nmol/l for the dental assistants	Dentists: Dose related impairment in 4 out of 8 tests of motor coordination, 1/3 tests of attention, 2/3 tests of working memory 0/2 of perception, 1/1 of perceptual speed, 0/2 of cognitive flexibility. Dental assistants: Dose related impairment in 3 out of 8 tests of motor coordination, 1/3 tests of attention, 0/3 tests of working memory 1/2 of perception, 1/1 of perceptual speed, 1/2 of cognitive flexibility. Polymorphies in genes for coproporhyrinogen oxidase and BDNF were related to performance but no interaction with mercury was seen.
(1;25) Scotland, cross sectional	180 dentists and 180 university staff members-. Mean age dentists 39.3 (23-62) yr /controls 32.1 (21-63) yr	15.6 (0.5-39 yr of practice. Urinary Hg Dentists 27.1 (.21-219.5) nmol/L. Controls 7.0 (0.01-44.1) nmol/L	8 tests. Dentists had lower scores in vigilance, but higher in choice reaction time (corrected for age and sex). In 14 symptoms/conditions dentists had more reported kidney disorders and memory disturbances. None of the outcomes showed correlation with measurements of urinary mercury.
Echeverria et al 1998 (62)	34 dentists and 15 dental assistants . 34 males and 15 females, mean age 29 yr.	U-Hg dentists 4.5 (SD 2.6)nmol/l Dental ass. 5.1 (4.7) nmol/l. After chelation 50.4 (36.9) nmol/l Dental ass. 40.4 (30.0) nmol/l	Finger tapping, hand steadiness, switching attention, Trail mark A and B, correlated to U-Hg, expected direction, visual retention opposite. Nearly the same results U-Hg after chelation.
(61), USA 1991-1996, cross-sectional	Covering 6 studies conducted during the last 6 yr attendants at the annual dental conferences. The number of participants in each study varied from 20 to 75. Mean age 50 yr (SD= 12). from 46 to 53 yr in the individual studies	230 dental professionals (approx. 110 with U-Hg levels exceeding 100 nmol/L[a], (ranged 100-740 nmol/L) the rest with undetectable U-Hg level.	Intentional Hand Steadiness Test (IHST); (n= 169) Significant decrease with mercury level ($p<0.001$). Finger Tapping (n= 94) No effect of mercury ($p=0.17$) Hand Tremor (n= 95) No effect of mercury. The One-hole Test (n= 86) No effect of mercury ($p=0.68$) NES Simple Reaction Time (n= 106) No effect of mercury (0.28).

(67), Sweden, cross sectional	44 dental personnel (22 dentists, 22 dental nurses) working in teams at six dental clinics/ 44 hospital employees (mainly physicians and nurses) without occupational exposure to mercury	On average, the dental personnel had worked in dentistry for 20 yr. (range 8-35). Median age of the exposed group was 43 yr. (range 29-59) and 45 yr. (range 29-62) for the controls. The median time-weighted average air Hg (TWA) was 0.0022[b] mg/m^3 for the dental nurses, and 0.0018[b] mg/m^3 for the dentists. Median U-Hg for dental personnel was 24.2 nmol/L[c] and 16.8 nmol/L[c] for controls.	The scores in the EPI (Eysenck Personality Inventory) questionnaire did not differ between the two groups. In the POMS (Profile of Mood Scales), the dentistry group displayed a statistically significant higher score than the controls for only anger (*P*= 0.034).
Nilsson and others 1990 ((43)	192 dentists (53 female) and 321 female dental nurses and other personnel. 41 controls (28 female)	Dentists 17 (2-64) nmol/L Nurses (public) 20(2-48) nmol/L Nurses (private) 30 (2-170) nmol/L	No differences in four symptoms (loss of appetite, tremor, insomnia, and anxiety) between subjects with low and high levels of urinary mercury. No difference between any of the groups and controls.
(54), Mexico cross sectional	10 female mercury-exposed dental technicians/ 13 unexposed laboratory technicians	Mean yr of age for dental technicians was 20.2 and 36.4 for the control group. The mean urinary mercury excretion before administration of the chelating agent DMPS, was 6 times greater than that of the non-dental controls, and 15 times greater after DMPS administration. The mean urinary mercury concentration before administration of the chelating agent DMPS, was 10 times (148.5[a] vs. 15.0[a] nmol/L) larger than that of the non-dental controls, and 13 times (2,405[a] vs. 186[a] nmol/L) greater after DMPS administration.	Based on the urinary excretion of mercury after the DMPS challenge, multiple-regression analyses found that the time to match symbols with digits (digit-symbol substitution) and the time to switch between tasks (the switching task) were increased and thus adversely affected by exposure to mercury (*P* ranging 0.00-0.06). All the mood scales deteriorated with exposure, but only the differences in scales for tension, anger and confusion were statistically significant.

(60), USA 1991, cross-sectional	19 dentists with U-Hg levels exceeding 95 nmol/L[a]/ 20 dentists with non-detectable levels of Hg in their urine.	Mean age of the exposed group was 52 yr. (SD= 15) and 45 yr. (SD= 13) in the unexposed group. Yr in practice in the exposed group; 25 yr. and 21 yr. in the unexposed group. The mean on-site Hg concentration in urine was 182 nmol/L[a] (SD= 100 nmol/L) among exposed dentists and was non-detectable among the control group.	The total mood score (Profile Of Mood States), especially for tension, fatigue, and confusion, was significantly associated with urine Hg levels ($P< 0.05$), and so was the verbal skills (NES Vocabulary) ($P= 0.01$). Individual tests evaluating cognitive (The Digit Span Test, The Switching Task, The Simple Reaction-time Test (NES), Symbol-digit Substitution (NES)) and motor (The One Hole Test) function changed in the expected directions but were not significantly associated with U-Hg. However, the sum of ranked scores measures for these function groups were associated with urinary Hg levels ($P< 0.04$), i.e. reduced performance with increased exposure.
{Ngim, 1992 268 /id}, Singapore, cross sectional	98 dentists exposed to metallic mercury in their work/ 54 controls selected from staff at the National University of Singapore matched for educational level.	The average age for dentists was 31.7 yr. The average yr of work were 7.4 for dentists. The TWA (time-weighted average) exposure intensity was 0.017 mg/m^3 mercury.	Analysis of covariance showed that the neurobehavioral test performance (Digit Span/short-term memory, Symbols Digit/visual motor speed, Grooved Peg Board/manual dexterity) was poorer in the exposed group as compared to the controls. The difference was statistically significant ($P= 0.0001$).
(56), USA, cross sectional	13 female dental auxillary workers (E group) with elevated head mercury levels compared with 13 dental auxiliaries (C group) with no measureable mercury levels and comparable age, education, and number of years employed in dental work.	Head hair mercury levels ranging from 25-115 μg/g. The mean age for this group was 41.15 (SD = 12.98) yr and the mean number of yr employed in dental work was 15.31 (SD = 5.05).	General intellectual functioning, as measured by the WAIS, was not affected. Comparisons of times for the non-preferred hand of the E and C groups to complete the Grooved Pegboard with the Mann-Whitney *U* statistic yield a one-tail probability of 0.025, non-significant at an overall or family error rate, of $\alpha = 0.05$ with the Bonferroni multiple testing adjustment. No significant differences between groups were found with the Rey's AVL and PASAT. Performances on BGT and Finger Tapping were similar for the E and C groups. Symptom dimensions were compared with two-sample *t* tests to determine differences between the two groups, and obsessive-compulsive ($P< 0.03$), anxiety ($P< 0.03$), psychoticism ($P< 0.03$), and general stress index ($P< 0.04$) were found to be significantly elevated in the E group at the $P< 0.05$ level.

(55), USA, case-control	298 male dentists took part in the study (mean age 54). 26 with elevated Hg levels (> 20µg/g head and wrist values) and ranked within the top 20% of the study population were then assessed by neuropsychological tests/ 17 dentists with no detectable tissue mercury levels.	Head hair mercury level (µg/g) of the 298 dentists: approx. 73% <20, 15% between 21-40, 7% between 41-60, and 5% > 61. Wrist mercury level (µg/g) of the 298 dentists: approx. 90% <20, 5% between 21-40, 3% between 41-60, and 2% > 61.	The full-scale intelligence quotient scores (WAIS), the finger-tapping-rate, and the grooved-pegboard tests did not indicate differences between the high-mercury and the control groups. A Bonferroni *t* statistic for multiple comparisons showed that the Bender-Gestalt test values of the high-mercury group were significantly different from those of controls ($P < 0.01$).

[a]µg/L converted into nmol/L
[b]µg/m^3 converted into mg/m^3
[c]nmol/mmol creatinine converted into nmol/L

4 Effects of mercury on neuropsychological performance and symptoms

Several studies have addressed the difference between groups of present or previously mercury exposed workers and controls according to neuropsychological symptoms. A critical review of the studies up to 1996 has been made by Ratcliffe (68). Three recent meta-analyses have systematically tried to summarize the results (69-71).

4.1 Critical review and metaanalyses

Ratcliffe et al made a critical review of 91 studies of all the different health effects of chronic occupational exposures (68). They used a preset series of criteria for the quality and they only regarded 13 studies fulfilled these. Five studies were regarded as positive all regarding neurological effects (55;72-75). The old study by Shapiro was the only dental study regarded conclusive (55). Besides, acute neurological and pulmonary effects had been convincingly reported in four older case studies with very high exposures. The authors did not conclude about the intensity or length of exposure to inorganic mercury required for these acute effects.

Meyer-Baron et al. 2002 (69) made an analysis of 12 epidemiological studies which provided data for analysis of current exposure to mercury on neuropsychological performance (54-56;59;73;74;76-82).

In a later paper they made a further analysis to explore a dose response relationship (70) adding 6 studies with a separate analysis of persons with former but not actual exposure (73;79;83).

The 12 studies were selected from originally 44 studies by a set of criteria requiring the tests used also having been used in two other studies, report of the mean and standard deviations of the test, and some control of confounders. Five of the included studies concerned dentists or dental assistants while the rest mainly included workers at chlor-alkali plants or lamp production. All studies except one were cross sectional. Fourteen different tests including 20 measurements were considered roughly categorized into the underlying functions, attention, memory, construction/reasoning, and motor performance. Effect size was normalized as the

mean difference between groups divided by the standard deviation (comparable to z-score). Out of the 20 measures 13 showed to have a homogeneous effects across the different studies.

Significant differences between exposed persons and controls were seen in one out of 5 measures of attention, where the very frequently used simple reaction time and symbol digit showed heterogeneity. In memory the two measures in Benton visual retention and word recognition were significant while in construction tests only block design showed an effect, which size was considerable smaller than the rest of the significant effects. Of the two motor performance tests included the peg board test was significantly lower in exposed persons compared with the controls.

The exposed persons in the included studies had mainly mean urinary values of 72- to 270 nmol/L but the individual study groups had mean values up to 1150 nmol/L. In an attempt to look at a possible threshold for an effect the effect sizes in the different tests in the individual study group were compared between the 28 exposed groups with mean exposure level above 600 nmol/L and the 167 below this value.

A clear distribution with larger effect sizes in the groups with levels above 600 nmol/L indicates a threshold for an effect below this value. A similar analysis comparing the 87 tests in groups with urinary mercury above 126 nmol/L with the 80 study with mean values below 126 nmol/L showed a weak non-significant tendency to a higher effect in the high group.

This may indicate, that if there is a threshold for an effect of long term ongoing mercury exposure this will lie well below 600 nmol/L while it can not be stated whether it is below or above 126 nmol/L.

A further analysis of the dose response relation was made by the same group in an attempt to estimate the effect size as a function of exposure. Two of the studies had considerably higher exposure than the rest, 730 and 1150 nmol/L, respectively (76;84). Only 11 studies were included in the mathematical analysis to test the relation between exposure and effect size in three domains, attention, memory, and motor performance.

The effect sizes were based on the regression lines in figure 2 of the report and converted from g Hg/g creatinine to nmol/L calculated to be 0.055 /100 nmol/L (not sign.) for attention, 0.0.110 /100 nmol/L (p=0.04) for memory, and 0.136 /100 nmol/L (p=0.002) for motor performance. In a pooled analysis the difference

between the effects of exposure on the three domains was significant. Omitting the study with a considerably higher exposure than the rest (76) in this analysis did not change the results and including the three studies with subjects studied after cessation of exposure did not change it either. In this analysis no attempt to estimate a threshold value was made.

Effect sizes mentioned in these metaanalyses are Z-scores calculated as the difference between the exposed and the non-exposed group divided with the pooled standard deviation within the groups. They are arbitrary units but according to Cohen they roughly can be categorized as a value of 0.20 as “small”, 0.5 as “intermediate”, and 0.8 as “strong” (69). However the use of these values have been criticized Rothman (85) for being more misleading than explaining.

Rohling and Demakis made a meta-analysis of a larger series of studies including those in the previous mentioned metaanalyses (71). Included were a number of studies only dealing with self-reported symptoms and some including neurophysiological variables. They included as independent factors time of exposure, time from last exposure, urinary mercury levels, blood mercury levels, inorganic, Hg^{+} vs. elemental mercury, Hg^{0}. Besides the studies of dental workers were compared with industrial workers (43;54;56;59;60;82). As in the previous study effect sizes were calculated as difference between exposed and non-exposed divided by the standard deviation (negative values mean that the exposed being inferior to the controls).

A vast number of effect variables were analysed where objective and self reported measures were mixed. The number of studies on which the variables were based varied from 2 to 42. Self reported symptoms showed larger heterogeneity than objective tests but also larger effect size (-0.30 vs. -0.22). In comparison with the two meta-analyses by Meyer-Baron the effect sizes were smaller, probably due to a larger heterogeneity in the vast number of studies and outcomes.

In the different domains psychomotor skills showed the most consistent difference between groups followed by psychological symptoms and cognitive functions while no significant difference was seen in the sensory/perceptual variables.

A number of correlation analyses were between a sum of all effects and various measures of exposure. Studies of current exposures showed larger values than former exposure (0.26 vs. 0.16), although the latter was still significant. The effect sizes decreased with the time from the last exposure in the formerly exposed groups.

On the other hand paradoxical effects were seen in the correlations between measures of exposure and the effect sizes. The levels of mercury in air and in urine did not correlate with the effects size and the length of exposure and mercury in blood showed negative (unexpected) correlation with effect size.

There was no difference between the effect sizes calculated from the five studies of dental personnel and the other studies despite a considerably (six times) lower exposure in the studies of dentals. The influence of gender was not analysed.

This vast and complicated meta-analysis primarily highlights the heterogeneity of the studies. It is in agreement with Meyer-Baron showing that a decrease in psychomotor performance seems to be the most consistent effect in chronic mercury exposure.

The missing correlation between urinary mercury and effects is clearly in contrast to the dose response analysis by Meyer-Baron et al. (70). The reason for this can not be seen from the articles, but the inclusion of subjective ratings may be of influence. Besides, in both analyses most of the studies were cross sectional and therefore very sensitive to selection, especially healthy worker selection.

The apparent higher sensitivity in dentists compared to other workers may be a genuine effect or may be due to the fact that the effect sizes for the single study was calculated as the mean difference divided by the standard variation and a more homogeneous group as dental personnel probably have a lower variability in performance than industrial workers.

In neither of the studies the influence of gender was tested.

The newer studies of dentists mentioned in chapter 3 were obviously not included. The study by Ritchie and by Jones would fit in while the study of Eccheverria would not be comparable as the measures of effect were calculated as internal dose response relation as no external control group was used.

4.2 Studies of the effect of past exposure

Within the above mentioned analyses four studies address the effects of several years after cessation of exposure. Two of the studies were dealing with persons with former intoxications (77;86). The relevance of these studies is low, as the only message is that a group of persons which sometimes in the past got a diagnosis of intoxication based not well defined criteria still is different from a control group several years later.

Mostly interesting are the two Norwegian studies of former chlor-alkali workers. They have a similar setup and are dealing with two groups of which one has been exposed with urinary values about 539 nmol/l (79) and 98 nmol/L (87). They were well conducted and there were excellent repeated measurements of urinary mercury during the exposure.

A striking difference was seen as a number of performance tests were impaired in the study of Matthiessen with the high exposure while no difference in neither symptoms nor neuropsycholgical performance tests were seen in the latter. Despite these negative findings an improvement in digit span was seen in those who formerly had had the highest exposure levels.

The older study of Letz et al (83) did in a much older population only find a decreased nerve conduction velocity, but the study was limited by very crude exposure assessments, and the use of performance tests in this age group is rare due to a much larger individual variability and influenced by more competing diseases.

The studies of Jones et al and Hilt et al referred in chapter 3 seem to fit in as a moderate past exposure gives rise to no or very discrete effects in performance (49;50).

4.3 Individual risk factors

The studies reveal different personal factors influencing the outcome. Age was the most prominent factor. Non of the studies, however have investigated whether an older group of workers are more or less susceptible to mercury exposure and only the study of Bast-Pettersen has been able to describe whether long term mercury exposure influence of the change, mostly decline, in neuropsychological function by ageing (87). They found no such effect, but in contrary a single indicator of reversibility.

The influence of gender has not been specifically investigated. Most of the industrial studies have predominantly included males, and gender has only been included in some studies as a confounder in the main analyses. The interaction between exposure and gender or in another way a possible difference in the susceptibility to mercury between males and females has not been tested. In the studies on dentists in chapter 3 neither has this been an issue, although the sex ratio in dentists makes it possible. In reviews of exposure to metals gender this has not been an important issue (88).

Some genetic risk factors have been studied in the recent dentist study by Eccheverria et al (64;65). In this large well defined group of persons a direct effect on

performance was seen of the polymorphism, but no interaction with the sensitivity to mercury at these very low levels. Whether it may be of importance at higher levels is not clear.

4.3.1 Confounding and bias

The studies have almost solely been cross sectional using control groups of various quality. This may give bias as what is intended to measure a biological effect of mercury really is a social difference between two more or less comparable groups of persons. A difference in the distribution of age, gender, and educational level has a considerable influence in several studies (1;9;86).

As the exposure usually needs to last for several years the selection of the study group is of major importance. Even though the eventual low dose has no direct acute effect in any trade a selection takes place whereby those who for one or another reason can not continue in the trade drop out before reaching a significant exposure leaving a survivor group to be studied. If this selection has something to do with a special exposure or an individually higher susceptibility. This leads to a "healthy worker effect" and investigating these survivors can seriously underestimate an effect of mercury.

In normal industrial jobs this selection is strong. Whether this is the case in dentistry has not been studied. It may be possible that a neurotoxic effect as tremor or ataxia may give serious problems in being a dentist. Besides several studies have excluded persons with neurological diseases, in which the exposure may be a partial cause.

4.4 Conclusions

A number of epidemiological studies have been made on the neuropsychological effects of inorganic mercury. They have studied the average impairment in groups and no effort has been made to suggest individual diagnoses.

According to dose response the main interest has been laid on the level i.e. urinary concentrations while the length of exposure has had surprisingly little room, although most studies have had at least five years exposure.

A detectable adverse effect on neuropsychological performance and specific symptoms is seen at a body burden expressed as urinary levels mercury about 5-600 nmol/L, both in actually exposed persons and in persons with previous exposure while no clear effect can be detected at 100 nmol/L. It can not be concluded

whether there is a threshold for an effect or an effect just is not detectable in epidemiological studies at the lower levels.

Both reported from meta-analyses and from the single studies it seems that at levels up to 500 nmol/L psychomotor performance tests and tests of hand steadiness are the most sensitive to mercury compared with tests of learning, attention, and other cognitive functions.

The few studies of persons with exposure several years back can not conclude on the course of the late effects. The studies, however, mainly tend to show either a lasting effect or some signs of reversibility. No information of an accelerating effect of mercury with increasing deterioration after cessation of exposure.

5 Reprotoxic effects

5.1 Definition of reproductive outcomes

The process of reproduction leads through several steps and toxic effects can influence on any of these. Therefore several different outcomes can be used in relation to reprotoxicology.

The possibility of conception is also called fecundity. This is interpreted as the chance of obtaining pregnancy in a menstrual cycle when pregnancy is intended. This may be measured by waiting time to pregnancy, i.e. the number of menstrual cycles from start of the planning until conception. These measures have frequently been used in epidemiological studies in relation to occupational exposures as welding and pesticides as well as life style factors both in females and males. Time to pregnancy may reflect both the probability of obtaining conception and very early miscarriages (89). Case-control studies of infertile couples are another way of investigating fecundity.

Foetal loss or miscarriages are frequently objects of reprotoxicological studies. The main problems are that miscarriages are frequent and as mentioned above early foetal loss often passes undetected. Later foetal losses are not as frequent and several factors may influence on the risk of miscarriage. Public registers are often incomplete and the information may rely on retrospective information. The Danish National Birth Cohort provides information about late foetal loss and pregnancy outcome in different jobs. (90;91). However data on job or trade are not consistent for dental personnel as the dental assistants were coded as office workers or receptionists. Other reproductive parameters used have been low birth weight either due to prematurity or growth retardation (small for gestational age).

Studies of umbilical cord blood at birth have shown, that the concentration in the child is at the same level as in the blood of the mother both in female dental workers (92) and in other exposed groups (93) (see table 5-1).

In the following the outcomes are reported separately although the different studies often report several outcomes. Most of the studies have been addressing exposure of female dental personnel, and a few studies have been looking at the effect of male exposure.

The results are summarized in table 5-1 at the end of this chapter. Detailed information about the studies are shown in appendix 4.

5.2 Spontaneous abortion/miscarriage

The newest larger study is the case-control study of Lindbohm and others (94). Cases were obtained from a linkage between the Finnish birth register and trade union files. Unexposed participants were pharmacists and secretaries in health care. No increased risk was seen in any of the dental groups. Within the dental group scoring for exposure to mercury amalgam showed that an intermediate group had a significant elevated risk which was neither seen in the low exposure group nor in the larger group with high exposure. The same picture was seen for exposure to the different types of acrylates and for disinfectants, but not for other exposures.

The other studies use self reported information on reproductive failures. Neither the Danish study from 1984, the recent Norwegian survey, nor the large American study showed any effect of exposure (9;95;96) while Dahl and Sundby 1999 found that dentists above 30 years of age had a higher rate of self reported spontaneous abortions than controls while those below had a lower rate than their controls (97). A Swedish register study based on data from 1980-81 showed rates of both spontaneous and induced abortions equal to the rates of all gainfully employed (98). The article reports data from a population study from the 60s where also expected rates of abortions (7 vs. 6.0 expected) were recorded.

The study of Rowland et al (99) primarily addressed nitrous oxide but in the analysis where the effect of nitrous oxide was not significant preparing more than 50 amalgams per week came out as a risk factor on level with age above 31 years and smoking more than one pack of cigarettes per day. A more detailed analysis of this has not been found.

In a Polish study (100) reproductive outcome was correlated with mercury concentrations in scalp and pubic hair showing a correlation between hair concentrations and the rate of miscarriages. The study has extensive measurements of hair samples with a few very high values and a considerable inconsistency between scalp and pubic hair values. The recruitment of the exposed persons and controls is not well described.

Outside dentistry a few relatively small studies do not give any conclusion of the effect of mercury on the rate of miscarriage (101-103).

5.3 Fecundability/infertility

Rowland et al interviewed in 1987-88 408 dental assistants selected from 4.856 responding to a mailed screening questionnaire (104). The material is a subset of the study of congenital malformations due to nitrous oxide (99). The selected persons had been pregnant within four years prior to the screening. Waiting time to pregnancy for the most recent pregnancy irrespective of outcome was used in the analyses and information on a series of self reported exposures was obtained. The different procedures in a dental clinic were scored according to hygienic standard thereby giving an individual score of poor hygiene factors (i.e. hand contact (manually mixing and pressing out excess mercury in a cloth, no gloves, no cover on amalgamator, carpet in operating room, history of spills). An analysis was made including number of amalgams prepared per week and number of poor hygienic factors (three categories). As seen in the table fecundity rate decreased by a combination of many amalgams prepared and poor hygienic measures. This interaction can be interpreted as that a series of poor hygienic practices are needed to elicit an effect of mercury on fecundity.

The results can be interpreted as a possible effect of mercury but the hygienic measures may reflect a latent factor of poor hygienic standard or there may be some recall bias. However the results were the primary goal of this study and the analyses seem to be well conducted.

Dahl and Sundby analysed for the trend in fertility over time but no difference between the four decennials from 1951 to 1990 was seen (97).

According to infertility only the small study of Jones et al showed a non significant elevation of self reported conception difficulties (50). An older US study of female dentists showed a lower rate of infertility than in hospital doctors (105).

In case-control studies of infertile couples (see Table 5-4) an increased rate of self reported exposure to mercury, lead, or cadmium was seen in a Danish study. Analysing for jobs, however, female dentists or dental assistants did not show elevated risks of infertility (106). Choy et al found slightly elevated blood mercury levels in infertile couples in Hong Kong, related to intake of seafood but not to occupation (107).

The study of Sikorski et al reported a higher prevalence of menstrual disorders in 45

dentists than in 21 controls and the rate was correlated to scalp hair mercury (100). Outside dentistry workers exposed to mercury in a lamp factory showed an elevated rate of menstrual abnormalities in comparison with a control factory (rate ratio=1.4) (101).

5.4 Congenital malformations

A comprehensive register study in Sweden of pregnancy outcome in dental personnel looked at 8.157 infants born in 1976 and in 1982-86 (98). The study looked at stillbirths, low birth weight, perinatal death, and congenital malformations. The observed rates were compared with expected numbers calculated from the national register standardized for year of birth, parity, maternal age, and infant sex.

Dentists had slightly lower rates of major congenital malformations than expected, while dental assistants and dental technicians had rates as expected from the national base. No specific pattern in the type of malformations was seen.

A study of 220 infants born in 1967-69 with neural tube defects did not have dental personnel as parents (expected number was 0.5) indicating that no gross excess risk for this serious malformation was detected. A Norwegian study of children born 1970-1993 found 7 neural malformation in dental personnel compared with 5.2 expected (ratio 1.4 (CI 0.61-2.77) (108).

The other surveys of dental personnel did not show unexpected risks of congenital malformations (9;50;95;105;109). None of the other studies of mercury showed any specific malformations, either (101;102;110).

5.5 Low birth weight

In dental assistants the Swedish register study showed a slightly higher rate of low birth weight (<2,500 g), with a risk ratio of 1.2 (CI 1.0-1.3) while dentists and dental technicians had ratios of 0.9 and 0.8, respectively (98). None of the other studies showed any effect (50;101;105).

Hujoel et al found that pregnant women who during pregnancy had dental amalgam replaced and thereby a possible exposure, had a paradoxically low rate of low birth weight (111). This relation was not significant after correction for socio demographic factors and therefore probably an indication of better dental health in these persons.

5.6 Stillbirths and perinatal deaths

Perinatal deaths cover stillborn infants and live borne who die within 7 days.

Dental personnel in the Swedish study had a decreased rate of stillbirths and perinatal deaths (within 7 days) in comparison with national rates (risk ratio 0.6 (0.5-0.9)). The other studies covering this did not show any unexpected rates (50;101;102;105). Sikorsky did not show differences between the groups but a relation with hair mercury, which probably mainly reflects organic mercury (100).

5.7 Neuropsychological development in offspring

Compared with the large studies of neurodevelopmental effects of organic mercury only a few studies have addressed this in exposure to metallic mercury (6). According to dentists only the Norwegian survey and the New Zealand study have considered this. Hilt et al reported a lower frequency of children with need for learning aid or psychological service than the controls, especially in children of dentists (9) while the small study by Jones et al reported 5/38 vs. 2/30 with learning difficulties and 2/38 vs. 1/30 in the controls with reported delayed development (50).

5.8 Male exposure and effects in offspring

Male fertility covers several different measures of the function of the male reproductive system. However, according to the results of pregnancies with fathers with mercury exposures only a few have been traced.

The US study by Brodsky addressed male dentists' exposure and pregnancy outcome of their wives (95). No difference between those with high and low exposure was seen.

A French study of males employed at an chlor-alkali plant showed a dose related increase in miscarriages with urinary levels, although the effect in each exposure class did not reach significance (112). The median level of 225 nmol/L was relatively modest.

A US study investigated persons from a production plant with very high exposures (probably more than 1.000 nmol/L) although the paper does not give an opportunity to calculate the values (110). In the raw analyses a dose related increase in miscarriages of about 50% in the highest group but in an analysis correcting for maternal factors this effect did not reach significance. In the study no effect on

congenital malformations was seen.

5.9 Discussion and conclusion

An evaluation of the reprotoxic effects of elemental mercury in humans, especially dental workers is limited by the varying quality of the studies, especially according to exposure. Due to the very frequent outcomes as miscarriages and congenital malformations the comparisons are difficult. Besides, factors in the mother as previous reproductive history, age and sociodemographic factors add to the difficulties.

Based on larger, well conducted register studies in Sweden and Norway (98;108) the normally used outcomes of reproductive problems were not different from a normal population. The case-control study of Lindbohm et al found an indication of some exposure related effect on miscarriage, but also to other exposures and the total rate in comparison with controls was not elevated (94).

Older Danish data does not support an increased risk in dental personnel (96) but no register based study has been carried out in Denmark.

The neuropsychological development of children of mercury exposed parents has only been scarcely investigated. The studies are difficult and the few studies do not give any conclusion.

Only very brief indicators of increased abortions in dental personnel are traced, while the largest registers studies did not show any excess risk of negative reproductive outcomes. Studies with higher exposures in other trades do not confirm an effect.

If there is a genuine effect in dental personnel several different exposures may be of importance, firstly nitrogen oxide. No Danish register studies have been carried out. Therefore to evaluate whether the findings in other countries can be reproduced, a historic cohort study of registered reproductive positive and negative outcomes will be of interest.

5.10 Table for chapter 5

Table 5-1 An overview of the studies of reprotoxicological effects in dentistry and to metallic mercury in other industries. More detailed tables are shown in appendix 5.

Study, year	Mercury levels in women and offspring	Abortion/ miscarriage (M= male exposure, F= female exposure)	Fecunda-bility	Infertility/c onception difficulty	Menstrual disorders	Congenital abnormalities/ malformations in offspring (M= male exposure, F= female exposure)	Low birth weight infants (<2,500 g)	Perinatal death (still birth)	Neuropsycho-logical development of offspring
(9), 2006 cross sectional, Norway Dentistry		F. Self-reported. No sign. diff. (P= 0.275-0.940)				F. No unexpected risks			Lower frequency of children with need for learning aid/psychological service in the dental group
(50)case control 30-year follow-up, New Zealand, Dentistry		F. No sign. diff.		No sign. diff.		F. No sign. diff.	No sign. diff.	No sign. diff.	No sign. diff. (learning difficulties, developmental delay)
(94)case control, Finland, Dentistry		F. No increased risk compared with controls. In the dental group exposure to intermediate levels of amalgam had sign. elevated risk compared with low/high exposure							

Study, year	Mercury levels in women and offspring	Abortion/ miscarriage (M= male exposure, F= female exposure)	Fecunda-bility	Infertility/c onception difficulty	Menstrual disorders	Congenital abnormalities/ malformations in offspring (M= male exposure, F= female exposure)	Low birth weight infants (<2,500 g)	Perinatal death (still birth)	Neuropsycho-logical development of offspring
(111), 1993-2000 case-control, USA, dental filling placement during pregnancy							The odds for a low birth weight infant were sign. lower among women who had one or more amalgam fillings replaced (OR 0.65, CI0.46-0.92)		
(97;113)1991 cross sectional, Norway, Dentistry		F. Dentists > 30 yr. of age had a higher rate of self reported spont. abortions (OR 2.4)	No statistically sign. difference						
(108), 1970-1993 register study, Norway, Dentistry						F. 7 neural malformations in dental personnel compared with 5.2 expected (ratio 1.4 (CI 0.61-2.77)			
((99;104)1987 cross sectional, USA Dentistry		F. Preparing more than 50 amalgams/week was = a risk factor of 31 yr. of age and smoking > 1 pack of cigarettes/day	Fecundity rate decreased by a combination of many amalgams prepared and poor hygienic measures						

Study, year	Mercury levels in women and offspring	Abortion/ miscarriage (M= male exposure, F= female exposure)	Fecunda-bility	Infertility/c onception difficulty	Menstrual disorders	Congenital abnormalities/ malformations in offspring (M= male exposure, F= female exposure)	Low birth weight infants (<2,500 g)	Perinatal death (still birth)	Neuropsycho-logical development of offspring
(109), 1968-1980, case-control, USA, Health care						F. Risk ratio for any congenital defects was 1.35 (CI 0.70-2.61). M. Risk ratio for any congenital defects was 0.98 (CI 0.40-2.36)			
(98)1976-1986 register study, Sweden, Dentistry						F. No differences between the observed and expected numbers	Dental assistants had a higher rate of low birth weight (risk ratio 1.2 (CI 1.0-1.3), and dentists and dental technicians a lower rate	Dental personnel had a decreased rate of stillbirths/perinatal deaths compared with national rates (risk ratio 0.6 (CI 0.5-0.9)	
(100)cross sectional, Poland, Dentistry		F. Dentists with past reproductive failures had sign. higher Hg levels in hair (scalp P= 0.0038, pubic P= 0.00032)			Sign. associated with no. fyr. worked in dentistry (P= 0.0052) and level of Hg in scalp hair (P= 0.0444)	F. Past reproductive failures (incl. cong. malf) were sign. associated with Hg levels in hair (scalp P= 0.0038, pubic P= 0.00032)		Past reproductive failures (incl. stillbirth) were sign. associated with Hg levels in hair (scalp P= 0.0038, pubic P= 0.00032)	
((95)1968-1978 historical follow-up/retrospective, USA, Dentistry		F. No statistically sign. effect. M. No statistically sign. effect				F. No statistically sign. effect. M. No statistically sign. effect			

Study, year	Mercury levels in women and offspring	Abortion/ miscarriage (M= male exposure, F= female exposure)	Fecunda-bility	Infertility/c onception difficulty	Menstrual disorders	Congenital abnormalities/ malformations in offspring (M= male exposure, F= female exposure)	Low birth weight infants (<2,500 g)	Perinatal death (still birth)	Neuropsycho-logical development of offspring
(96), 1980 cross sectional, Denmark, Dentistry		F. No sign. effect of exposure							
(105), 1928-1977, historical follow-up, UK, Dentistry		F. The abortion rate in the dentist group was sign. higher in general (P< 0.05) and highly sign. (P< 0.001) at first pregnancy		Sign. (P< 0.02) lower frequency of infertility in the dentist group compared with doctors		F. Frequency of malformations did not differ sign. from the control group	More babies were born at < 1.6 kg to working dentists than non-working dentists (P< 0.05). In general the rate was within the expected	The rate of perinatal deaths was within the expected	
(92), cross sectional, Norway, Dentistry	Sign. (P< 0.05) higher Hg content in placenta, chorion membrane and amnion membrane in the exposed								
(102)1948-1977 cross sectional, USA, Thermometer factory		F. No sign. difference				F. The risk ratio estimate was 1.333 compared to non-exposed workers		No statistically sign. difference	
(93)cross sectional, China, Lamp factory	Sign. (P< 0.05) positive correlation between inorganic Hg level of maternal blood and umbilical cord blood								

Study, year	Mercury levels in women and offspring	Abortion/ miscarriage (M= male exposure, F= female exposure)	Fecunda-bility	Infertility/c onception difficulty	Menstrual disorders	Congenital abnormalities/ malformations in offspring (M= male exposure, F= female exposure)	Low birth weight infants (<2,500 g)	Perinatal death (still birth)	Neuropsycho-logical development of offspring
(112)1984 cross sectional, France, Chloralkali plant		M. The risk of spontaneous abortion rises sign. with U-Hg conc. (P< 0.05)							
((110)1952-1966 retrospective cohort study, USA, Plant		M. The average odds ratio for miscarriage was 1.57 (P= 0.008)				M. No statistically sign. difference			
(101), cross sectional, Italy, Lamp factory		F. Rate ratios compared with controls were 1			Rate ratio of abnormal cycles was 1.4	F. More cases of congenital dislocation of the hip, could be due to regional differences.	No difference	The rate of perinatal deaths was within the expected	
(106), 1977-1981 case-control, Denmark, exposure to lead, Hg, cadmium				The exposed had 2-3 times the risk of idiopathic infertility					

6 Conclusions

The primary goal for this review has been set from the description of the goals stated in the notice from the Danish Health and Safety Research Fund (see appendix 1a and b): "There is a need for clarification of the possible course or relationship between exposure to metallic mercury, especially in the low doses which have been documented within dentistry, and the development of toxic symptoms or complaints within the neurological or neuropsychological area." This has been supplied with a number of specific questions stated in the notice.

The response to the questions have been made by discussing the main areas related to exposure and effects leading to the summary and suggestions for further research in the end of this chapter.

6.1 Exposure to mercury in dentistry.

The exposure to metallic mercury in dentistry has been monitored in different countries, especially Norway and to some degree in Sweden from the 60´s. From mid 70´s a large number of measurements of urinary mercury are available. Only few and unsystematic Danish measurements have been found.

The urinary mercury is the best documented measure of exposure. The mean levels in dental personnel in the period up to 1969 were 160-320 nmol/L but with considerable individual variations with 10% of the measurements above 500 nmol/L. About 1980 Norwegian values were decreased to about 43-50 nmol/L based on a large number of measurements and the levels furthermore decreased to 22 nmol/L in the period 1990-2000. Later British and US surveys show values at these levels or lower. Remarkably Swedish studies from 1970-90 showed values in general 50% lower than the Norwegian measurements in the same period. The permissible limit in most European countries is 200 nmol/L

Comparing dentists and dental assistants the contemporary levels were nearly the same, while the smaller group of dental technicians up to 1984 had values about 100% higher than the two larger groups.

Some differences in urinary mercury could be attributed to the work practices and the furnishing of the clinics. Urinary mercury increased with the number of fillings

handled with a variation from 27 to 48 nmol/l (80%), while having wooden floor material showed an increase of about 30% in comparison with tiles or linoleum. Other characteristics of the clinics were of less importance in these older studies. No systematic difference between males and females was seen, which could not be attributed to the work function.

The immediate exposure measured as air concentrations in the breathing zone could give a better description of the sources to the exposure at different work processes in dentistry. A number of older studies from 1957 to 1980 showed that for the dentist drilling out old fillings is a main source of inhaled mercury with occasional exposures as high as 2 mg/m^3, but mainly about 0.15 mg/m^3. Using a high volume suction device decreased this exposure by a factor 10-50. Inserting the fillings gave lower concentrations.

Contamination around the chair gave rise to elevated air mercury levels in comparison with other areas in the clinics. In the area around the amalgam mixers and the waste storage the concentration were at the same levels as around the chairs. Ventilation did have some effect, but much less than the variation due to differences in work processes.

According to procedures preparing amalgam mixing amalgam manually in mortars etc. gave higher values than closed systems while using prefabricated capsules decreased the number of high concentrations measured even more. The number of reported spills has been correlated with the urinary concentration of mercury but direct causal relationship has not been documented. A direct effect is probable but spills may also be an indicator of poor hygienic measures in general.

Cupper amalgam has been a special issue, during heating short periods of high concentration of mercury could be detected in the air, but after a few minutes reversing to background levels. Very few measurements have been made and no studies of the impact of this procedure on urinary mercury have been reported.

Exposure to metallic mercury is predominantly by inhalation. The dermal uptake has only been briefly studied. However, the uptake is probably only a few percent of the inhalation and will be reflected in the urinary concentration. Dermal uptake when moulding and squeezing amalgam in the hands does therefore not constitute a hidden problem.

6.2 Health effects of mercury in dentistry

Acute mercury intoxication is characterized by a number of neurological and neuropsychological symptoms and the problem has been to which extend these effects can be detected from lower exposure. Very few genuine mercury poisonings has been reported in dentistry and many of the symptoms of intoxication have been very unspecific. Therefore the effects of exposure to mercury have mainly been studied by detecting minor impairments in various neuropsychological functions in comparison with unexposed persons. A series of these studies have been conducted in dentistry related to the urinary mercury or compared with external control groups.

Three major studies are of most interest. In a study from Singapore dentists with exposure to mercury corresponding to urinary values about 125 nmol/L showed impaired performance in a number of functions compared with the control group (59). A comparison of two subgroups of dentists with levels of 240 and 75 nmol/l, respectively, showed more impairment in the highest group. A Scottish study of dentists with an average of 27 nmol/L ranging up to 220 nmol/L showed no difference from a control group (1).

A comprehensive US study of male dentists and female dental assistant showed very low levels of mercury, in average 16.5 nmol/L and 9.9 nmol/L, respectively, levels well within the normal levels for US citizens without occupational exposure (64;65). The highest single value was 100 nmol/L, Within these groups correlations between urinary mercury and impairment in performance in several neuropsychological functions were shown. Effects were predominantly found in tests of psychomotor functions but also in other areas. In the studies the impairment of the performance was related to the actual level of exposure, while the length of exposure did not show any effect.

The studies may indicate an effect of actual exposure levels below 150 nmol/L in dental personnel. However, being cross sectional studies only associations are detected while the causal factor can not be stated. No information about the time course of the effects can be obtained from these studies.

The effect of urinary mercury on neuropsychological performance and symptoms has been analysed in three comprehensive metaanalyses based on studies from various industries including dentistry (69-71).

The studies in agreement show that the clearest effect of mercury is seen in tests of psychomotor performance and to a lesser degree in tests of memory and to much

lesser extent attention. Clear effects were seen after long time exposure to mercury with urinary concentration about 500 nmol/L while no effects have been detected at 100 nmol/L. A minor effect cannot be ruled out, as a an analysis of dose-response between 0 to 500 nmol/L does not indicate a threshold, but can be interpreted as linear relation between dose and effects. Despite a considerably lower average exposure in dentistry no difference in the calculated size of effect was seen in comparison with the studies from other industries. No relation with the duration of exposure and the effects were seen.

In the studies of past exposure the effects were smaller and decreased with the time from cessation of exposure. None of the studies showed any significant aggravation of symptoms in the years after cessation of exposure and studies of groups of persons with previous mercury intoxication showed either a partial regression of symptoms or steady state, but no indication of deterioration.

Regarding symptoms due to exposure to metallic mercury the results have been less clear. In the above mentioned studies the effects of performance clearly were more consistent than reported symptoms. The symptoms have varied showing no specific pattern and no relation to urinary mercury. Some correlations with self reported estimates of exposures during the previous years have been seen but all symptoms reported are very common in the general population and the knowledge about the potential hazard in the group studied definitely has been important.

6.3 Diseases long time after cessation of exposure

The present discussion whether dental assistants with a potential exposure to mercury in the past may have developed genuine mercury related diseases 20 to 30 year after the relevant exposure has been based on an increased number of symptoms in a small and a larger Norwegian questionnaire studies of dental personnel (2;9).

The larger questionnaire study showed an increased number of both neurological and general symptoms in dental assistants in comparison with controls while the dentists had lower frequency of symptoms than the controls.

The questionnaire studies a give a hint of the problems among dental assistants but the relation to mercury is questionable. Dentists had the same previous levels of mercury as the dental assistants and only spurious correlations with self reported exposure. Furthermore, a larger US study and a smaller study from New Zealand did not show any characteristic pattern of symptoms (50;66). Especially, the motoric symptoms (i.e.weakness and lack of coordination) expected from the studies of

neuropsychological performance were not prominent.

The questionnaire studies have later been supplemented with a small New Zealand study and a follow up of a subgroup from the Norwegian study where neuropsychological performance tests have been made (49;50). Neither study did show any clear relation with exposure. No relation between symptom score and performance was seen, either.

Based on the results of these studies supplied with the results of the studies of performance no clear pattern of a mercury related neurological disease can be found. Within the population there may be a small group with persistent signs and symptoms of a previous mercury intoxication due to excessive exposure probably followed by some signs of acute mercury intoxication.

On the other hand on group basis a slight impairment of especially motor coordination due to mercury exposure can not be ruled out emphasizing the importance of keeping the exposure to mercury at an absolute minimum.

6.4 Effects on reproduction

In the number of studies on the reprotoxic effects of metallic mercury in dental personnel a possible lower fecundability was seen in a single study, while other well conducted studies showed no effect. Large, well conducted register studies in Sweden and Norway, supported by studies in Denmark, US and New Zealand supported this. Stillbirths and low birth weight showed no excess frequency in dental personnel.

According to spontaneous abortions a recent case control study showed a slightly elevated risk in those with an intermediary self reported exposure to mercury, but not in the highest group or in the dental personnel in comparison with controls. Register studies in Sweden and Norway have not shown any excess risk

Therefore only single indicators of reproductive impairments due to exposure to metallic mercury can be found. However, as no Danish register study has been published the results of the ongoing study may add important knowledge.

6.5 In summary, evidence of causal associations

According to the evidence of causal relationship the key questions set in the posted requirements for the reference document (see addendum 1 b) can be answered as

There is strong evidence that the exposure to mercury in dentistry up to 1970 has

corresponded to average urinary values of 125-200 nmol/L with individual values ranging from 0 to 500 nmol/l. After this the average urinary values have gradually decreased to about 25 nmol/L with individual values rarely exceeding 100 nmol/L.

There is strong evidence that specific procedures have caused high air concentrations of mercury vapour. However, only the number of fillings has influenced urinary mercury levels, while no difference has been seen between dentists and dental assistants.

There is strong evidence that exposure to mercury corresponding to urinary mercury concentrations of 600 nmol/L on a group basis causes impairment of neuropsychological performance.

There is moderate evidence that the neuropsychological effects of exposure to mercury are either diminished or constant after cessation of exposure.

There is limited evidence that exposure to mercury in dentistry corresponding to urinary mercury concentrations of 150 nmol/L on a group basis causes slight impairment in neuropsychological tests.

There is insufficient evidence of specific neurological or neuropsychological diseases or complaints occurring several years after cessation of work-related dentistry mercury exposures.

There is insufficient evidence that any specific set of symptoms can be indicators of diseases caused by low levels of exposure to mercury in dentistry.

There is insufficient evidence that any distinct group with excess risk could be identified, neither according to sex nor genetic disposition.

There is insufficient evidence of any adverse influence on reproduction in dental personnel measured by fertility, miscarriages, retarded foetal growth, stillbirths, or congenital malformations.

6.6 Need for knowledge or further research

The information of exposure has mainly been based on foreign studies and a better description of exposure to mercury and other potential neurotoxicants in Denmark through the paste decades would be preferable. A construction of a model predicting exposure from various procedures in the various time periods could improve the risk

assessment.

The Danish Clinics of Occupational Medicine have examined a large number of dental assistants referred for possible intoxications. A systematic description of this material according to representativity and information about exposure, the symptoms and the occurrence of diseases may give a picture of the size and character of the problem.

The results of the ongoing register study will provide important information about the occurrence of diseases and reproductive outcome of the dental personnel.

A verification of the results indicating discrete, but significant neuropsychological impairment at levels within those seen in the general public would be important to elucidate the neurotoxic potential of metallic mercury.

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