Review of causes of irritant (toxic) contact eczema after occupational skin exposure

(Udredning af årsager til irritativt (toksisk) kontakteksem efter erhvervsmæssig udsættelse for irritative påvirkninger af huden)

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Title: Review of causes of irritant (toxic) contact eczema after occupational skin exposure.

Danish title: Udredning af årsager til irritativt (toksisk) kontakteksem efter erhvervsmæssig udsættelse for irritative påvirkninger af huden

Project number: 20150018092/3

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Financed by: The Danish Working Environmental Research Fund

Content

1 Foreword

The authors received a research grant from the Danish Work Environmental Fund in June 2015 following an international open call issued by the Danish Work Environmental Fund. The title of the call was "Review of causes of irritative (toxic) contact eczema after occupational exposure to irritative influences of the skin".

The reference document follows the special guidelines for performing and quality approval reviews in the form of a reference document in the field of occupational diseases provided by the Danish Work Environment Fund November 2010.

The report was prepared from November 2015 through May 2017 by a working group responsible for the database search, literature selection and drafting of the report.

Members of the working group were from the Danish Ramazzini Centre, Department of Occupational Medicine, Regional Hospital West Jutland – University Research Clinic, Herning, Denmark:

- Senior Consultant, PhD, Gitte Jacobsen (GJ),
- Senior consultant, Head of department Ole Carstensen (OC) and
- Associate Professor, PhD Kurt Rasmussen (KR).

Member of the working group from the Department of Dermatology, Aarhus University Hospital:

- Senior Consultant, PhD, Anne Bregnhøj (AB)

Contributions of the members of the working group:

GJ has contributed to concept and design of literature search, has performed the initial database search in collaboration with librarians, performed the literature selection, data extraction, and drafting of the report in close collaboration with the other members of the working group.

OC contributed to concept of design of literature search and selection, literature selection, data extraction and drafting and critically revising of the report for important intellectual content and final approval of the report.

KR contributed to concept of design of literature search and selection, literature selection, data extraction, critically revising of the report for important intellectual content and final approval of the report.

AB contributed to concept of literature selection, critical revising of the report for important intellectual content and final approval of the report.

In addition,

- MD PhD Marianne Kyndi and

- MD Rasmus Boe Mortensen,

both Danish Ramazzini Centre, Department of Occupational Medicine, Regional Hospital West Jutland – University Research Clinic, Herning, Denmark has contributed to the literature selection.

A preliminary first draft of the report was sent to the reviewers in November 2016 prior to a two days meeting where all the members of the work group were present and discussed the content of the report along with the two external reviewers:

- Prof. PhD Marléne Isaksson, Department of Occupational and Environmental Dermatology, Skåne University Hospital, Lund University.
- Prof. DMedSc Thomas L. Diepgen, Department of Clinical Social Medicine, Occupational and Environmental Medicine, University Hospital Heidelberg.

After the meeting, a final draft was submitted to the external reviewers who, as well as co-authors commented on the report. Their comments were included in this final version of the report.

2 Dansk resumé

Kontakteksem er den hyppigst anerkendte arbejdsskade i Danmark, med op mod 2.000 anerkendte tilfælde per år. Irritativt kontakteksem er en væsentligste årsag og udgør ca. 70% af tilfældene, ca. 1.300 tilfælde per år.

Formålet med denne udredning var på baggrund af en gennemgang af nyere danske og internationale forskningsresultater at belyse, vurdere og sammenfatte viden om årsagssammenhænge mellem irritativt kontakteksem og udsættelse for forskellige hudirritanter på arbejdet samt at vurdere sygdomsprognosen og eksponeringens (udsættelsens) betydning for prognosen.

Vi gennemførte en systematisk litteraturgennemgang basereret på PRISMA kriterierne (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). Vi foretog litteratursøgning i fire databaser (Pubmed., Embase, Web of Science og OSH-update) i vinteren 2015 og inkluderede artikler, der var forfattet på engelsk, tysk eller dansk efter 1979. Vi identificerede i alt 3.475 titler, og efter frasortering af dubletter, konferenceindlæg, studier baseret på enkelt cases og artikler publiceret på ikke inkluderet sprog fandtes i alt 1.373 unikke artikler i den indledende litteratursøgning. Derudover gennemgik vi referencelister fra de inkluderede studier samt fra tidligere litteraturgennemgange. De identificerede artikler blev med anvendelse af vores inklusions- og eksklusionskriterier gennemgået med screening af overskrifter, resumeer og læsning af artikler. Screening af resumeer og artikler blev foretaget, så alle blev gennemgået af to medlemmer af projektgruppen, der ved konsensus skulle være enige om, hvorvidt artiklen skulle medtages i den systematiske litteraturgennemgang. Centrale karakteristika for de enkelte studier blev ekstraheret og systematiseret i tabeller. Vi foretog kvalitetsgennemgang af hvert studie efter systematiske kriterier, hvor vi inddrog studiedesign, kvalitet af eksponeringsvurdering, sygdomsregistrering og hensyntagen til konkurrerende årsagsfaktorer. Baseret på denne gennemgang og en generel vurdering af studiet blev de enkelte studier tildelt overordnet kvalitetsvurdering med inddeling af studierne i høj, medium og lav kvalitet.

Litteratursøgningen resulterede i inklusion af i alt 50 artikler fra 45 studier, hvoraf to artikler blev identificeret ved gennemgang af referencer. 39 af de inkluderede artikler (34 studier) fokuserede på arbejdsmæssige risikofaktorer for irritativt kontakteksem og tolv havde fokus på prognose, et studie var inkluderet i begge udfald. Studierne var publiceret i perioden 1983-2015. En artikel var forfattet på tysk, de resterende på engelsk. Vi foretog ingen metaanalyser pga. væsentlige forskelle i definitioner på sygdomsudfald og eksponeringer.

Blandt de 34 studier med fokus på arbejdsmæssige risikofaktorer for irritativt kontakteksem var 11 forløbsstudier, heraf 10 fremadrettede studier og et bagudrettet studie. Herudover inkluderede vi et case-control-studie og 22 tværsnitsstudier. Diagnosen irritativt kontakteksem/irritative hudforandringer var verificeret klinisk af læge i 28 studier, heraf med lappetest i 11 studier. Lappetest er en forudsætning for

en sikker identificering af den delvist konkurrerende diagnose allergisk kontakteksem. I 14 studier var diagnosen baseret på selvrapportering hovedsageligt i spørgeskemaer, enten af primært håndeksem eller symptomer på eksem i relation til irritative eksponeringer, f.eks. vådt arbejde. I de fleste studier var størrelsen af eksponeringen for irritative stoffer selvrapporteret, og kun seks studier var baseret på kvantitative målinger eller semikvantitative vurderinger af eksponeringens størrelse. Vi klassificerede seks studier som værende af medium-høj kvalitet, 15 som medium kvalitet og 13 som lav kvalitet. Ingen af studierne blev vurderet som højeste kvalitet.

Ved undersøgelse af de enkelte eksponeringer delte vi disse i arbejde med udsættelse for vådt arbejde, arbejde med udsættelse for sæbe og desinficerede stoffer, arbejde med udsættelse for okkluderende (ikke åndbare) handsker, arbejde med udsættelse for forskellige kølesmøremidler og fedtstoffer hos metalarbejdere og arbejde med mekaniske udsættelser.

Vi fandt, at de inkluderede studier støttede en moderat sammenhæng mellem vådt arbejde og irritativt kontakteksem, specielt mellem hyppighed af håndvask og lettere irritativt eksem og specielt i kombination med andre hudirritanter. Flere studier rapporterede en dosis-respons-sammenhæng mellem irritativt kontakteksem/irritative hudforandringer, men det var ikke muligt af beskrive en grænseværdi for sammenhængen mellem irritativt kontakteksem og udsættelse for vådt arbejde. Vi vurderede, at der samlet er en stærk dokumentation for en årsagssammenhæng mellem vådt arbejde og irritativt kontakteksem.

Ved vurdering af studier der beskrev sammenhænge mellem udsættelse for sæbe og desinficerende stoffer, herunder med inddragelse af supplerende eksperimentelle studier, fandt vi, at der samlet er en moderat dokumentation for, at grad af udsættelse for sæber o.l. uafhængig af andre udsættelser giver en øget risiko for irritativt kontakteksem. Vi vurderer dog, at der er en stærkere dokumentation for en årsagssammenhæng mellem udsættelse for sæbe o.l. kombineret med andet vådt arbejde, f.eks. mængde af håndvaske og irritativt kontakteksem.

Resultater af de studier, der beskrev brug af okkluderende handsker uden samtidig udsættelse for andre hudirritanter varierede. Nogle beskrev negativ effekt af handskebrug, andre positiv og nogle kunne ikke påvise ændringer. På baggrund af de studier, der var af højest kvalitet, samt eksperimentelle studier, vurderer vi, at der er en begrænset dokumentation for en årsagssammenhæng mellem arbejde udelukkende med okkluderende handsker og irritativt kontakteksem. Formentlig bidrager brug af okkluderende handsker til irritative hudpåvirkninger ved samtidig udsættelse for andre hudirritanter, f.eks. vådt arbejde med håndvaske og brug af sæbe.

Ved vurdering af studier blandt metalarbejdere med udsættelse for forskellige kølesmøremidler og fedtstoffer fandt vi, at der er en moderat dokumentation for en moderat association mellem udsættelse for køle-smøremidler og irritativt kontakteksem, mens øvrige eksponeringer ved dette arbejde er beskrevet i for få studier til at dokumentationen kan vurderes.

Ved vurdering af studier, der beskrev udsættelse for mekanisk irritation, herunder studier med udsættelse for luftbårne fibre, blev der kun inkluderet i alt fire studier af medium og lav kvalitet. Tre af disse tydede på en moderat til stærk sammenhæng mellem irritative hudforandringer og mekanisk irritation, men pga. det lave antal studier og kvaliteten af disse vurderer vi, at den samlede dokumentation for en årsagssammenhæng til irritativt kontakteksem er beskeden.

De 12 prognosestudier var alle fremadrettede forløbsstudier, heraf 11 med klinisk verificeret diagnose af læge. Prognosen blev vurderet i forhold til komplet heling af eksem og bedring af eksem (heling og bedring) i opfølgningsperioden, der i studierne varierede fra 0,3-16 år og i forhold til eksponeringsændringer ved henholdsvis skift af job og ændring af arbejdsopgaver i det samme job. Tre studier blev vurderet som medium-høj kvalitet, fem af medium kvalitet, de resterende af lav kvalitet. Vi vurderede, at der er en stærk dokumentation for en dårlig prognose for komplet heling, hvor en stor andel ikke opnåede komplet heling. Den samlede andel med komplet heling i opfølgningsperioden varierede i otte studier mellem 18 og 72%. Der var en stærk dokumentation for en bedre prognose ved nedsættelse af eksponering for arbejdsmæssige hudirritanter ved skift af arbejde eller skift af arbejdsopgaver inden for samme ansættelse. Når prognosen blev vurderet i forhold til bedring i eksem, var denne sammenhæng ikke så udtalt, og sammenhængen blev vurderet som begrænset. Den samlede andel med bedring i eksem varierede i fem studier mellem 41 og 84%, og kun to af disse studier rapporterede om sammenhænge mellem bedring i eksem og skift i arbejde, hvor ingen af studierne fandt signifikante forskelle, mens kun et studie rapporterede en større andel med bedring ved skift af arbejdsopgaver inden for samme industri. På samme vis fandt vi, at sammenhængen mellem prognose for irritativt kontakteksem og varighed af forudgående sygdom henholdsvis varighed af forudgående udsættelse for hudirritanter udsættelse var begrænset.

Disponering for atopi, specielt en personlig historie med tidligere atopisk eksem (også kaldet atopisk dermatitis og børneeksem), er en velkendt sårbarhedsfaktor for irritativt kontakteksem/håndeksem. Vi medtog derfor studiernes registrering af disponering for atopi, og om studierne foretog analyser, hvor der blev taget hensyn til (justeret for) forudgående atopisk eksem, i vores kvalitetsvurdering af studierne. Selv om studier, der medtog disse oplysninger i de fleste tilfælde bekræftede en øget sårbarhed for irritativt kontakteksem blandt personer med forudgående atopisk eksem, tydede studier, hvor der blev foretaget udvidede analyser ikke på, at risikoen ved de irritative udsættelser udelukkende kunne tilskrives forudgående atopisk disponering/atopisk eksem. I nogle studier fandtes tilmed en stærkere sammenhæng mellem den irritative eksponering og kontakteksem, når studiet i analyser havde taget hensyn til atopisk disponering.

En række studier har ifølge tidligere oversigtsartikler rapporteret en øget sårbarhed for og hyppighed af irritativt kontakteksem blandt kvinder, der dog ikke har kunnet bekræftes i eksperimentelle studier, og hvor mistanken har været, at kvinder dels oftere arbejder i fag med højere grad af vådt arbejde og dels har en større grad af hjemlig eksponering for hudirritanter. Enkelte studier har også tydet på en sammenhæng mellem hjemlige eksponeringer og håndeksem/irritativt kontakteksem. Herudover har befolk-

ningsstudier tidligere beskrevet en nedsat sårbarhed for hudirritation med tiltagende alder, specielt blandt kvinder.

De inkluderede studier i denne litteraturgennemgang gav ikke væsentlig dokumentation for sammenhæng mellem køn, alder eller private eksponeringer for udviklingen af irritativt kontakteksem.

Der var en række begrænsninger i de inkluderede studier. Disse inkluderede risiko for misklassifikation (fejl-registrering) af såvel eksponering som sygdom. De fleste af studierne havde upræcise eksponeringsvurderinger, hvor oplysninger om eksponering var indhentet via spørgeskema, og der var kun få studier med mere præcise eksponeringsestimater ved målinger eller ekspertvurderinger. I en række studier var f.eks. udsættelse for vådt arbejde ikke sammenlignelig med sammenblanding af forskellige eksponeringer, og tidsperspektivet for eksponeringen var medtaget i selve definitionen på eksponering. F.eks. ved vådt arbejde, hvor der i den meget anvendte tyske definition indgår forskellige eksponeringer både for vand med og uden sæbe, og handsker, og som både medtager antal af f.eks. håndvaske og varighed af vådt arbejde i definitionen på, om der er vådt arbejde. Sygdomsudfald af formodet irritativt kontakteksem var også selvrapporteret i en række studier. Herudover var der varierende definitioner på irritativt kontakteksem i de forskellige studier, der vanskeliggør sammenligninger af sygdomsudfald. Selv om der i de senere år er kommet forskellige forslag til definition af irritativt kontakteksem, findes der ingen "gold standard" og ingen specifikke test for diagnosen. F.eks. har definitionen på irritativt kontakteksem i de senere år ændret sig fra at omfatte kontakteksem med en betydelig varighed, hvor lappetest har udelukket kontaktallergi, til at blive defineret ved en betydelig udsættelse for en kendt hudirritant, f.eks. vådt arbejde. Der er således en sammenblanding af diagnose og eksponering, der vanskeliggør vurderingen af eksponeringens betydning for diagnosen. Herudover er en del af de inkluderede studier tværsnitsstudier, hvor man ikke kan sige noget sikkert om årsagssammenhænge, da udfald og eksponering registreres samtidigt. Vedrørende prognosestudier var den væsentligste begrænsning, at sygdomsudfaldet ved opfølgning overvejende var selvrapporteret.

Alt i alt er der efter forfatternes vurdering af årsagssammenhænge mellem irritativt kontakteksem og forskellige eksponeringer i henhold til de kriterier, som er defineret af Arbejdsmarkedets Erhvervssikring og Erhvervssygdomsudvalget, en stærk dokumentation (+++) for årsagssammenhænge til eksponeringer ved vådt arbejde og til vådt arbejde kombineret med sæbe, en moderat dokumentation (++) for årsagssammenhænge til isoleret eksponering for sæbe og til udsættelse for kølesmøremidler og en begrænset dokumentation (+) for årsagssammenhæng til eksponering for mekanisk irritation og til eksponering for okkluderende handsker. Der er desuden en stærk dokumentation (+++) for en dårlig prognose af irritativt kontakteksem og for at ændringer i eksponeringer efter diagnose giver en bedre prognose, særligt når prognosen vurderes som komplet heling.

Baseret på de inkluderede studier er det ikke muligt at udregne samlede estimater for effekter af de forskellige eksponeringer, ligesom det ikke er muligt at angive grænseværdier (tærskelniveauer) for eksponeringer.

Med henblik på at afklare disse sammenhænge nærmere og afdække sikre eksponeringsniveauer er der et behov for større opfølgningsstudier med fokus på irritativt kontakteksem, hvor der foretages kvantitative målinger af eksponeringer og hvor diagnosen sikres ved veldefinerede kliniske undersøgelser.

Der er også behov for yderligere prognosestudier med anvendelse af registerdata og kliniske undersøgelser ved opfølgning.

3 Abstract

Objectives: Irritant contact dermatitis (ICD) is a major cause of occupational disease with up to 1300 annual cases compensated in Denmark mainly due to wet work, but also due to use of occlusive gloves, detergents, fresh food, oils and dirt. We aimed at systematically reviewing the relation between exposure to occupational irritants and ICD and the prognosis of ICD.

Methods: In a systematic review based on PRISMA (Preferred Reporting Items for systematic Reviews and Meta-Analyses) criteria and involving searches in four databases (Pubmed., Embase, Web of Science and OSH-update) 1,373 titles were identified. After screening of titles, abstracts and full text reading with application of our eligibility criteria 50 papers from 45 studies were included. Thirty-nine of the included papers (34 studies) had focus on occupational risk factors for ICD and twelve had focus on prognosis (one included both outcomes). Studies were published between 1983 and 2015. One paper was published in German, the remaining in English. Meta-analyses were not performed due to differences in reported outcome and exposures.

Results: Ten studies focusing on occupational risk factors for ICD were prospective cohort studies, one a retrospective cohort study, one a nested case-control study and 22 were cross-sectional studies. All studies on prognostic factors were prospective cohort studies. In 28 studies with focus on occupational risk factors for ICD or irritant changes, diagnosis was verified clinically, including patch tests in 11 studies, while 14 studies relied on self-reported outcomes. Only six studies provided quantitative or semi-quantitative exposure assessments. Six studies were classified as medium/high quality, 15 of medium quality and 13 of low quality.

Regarding wet work the studies supported a moderate association between ICD and wet work, especially for frequency of hand washing and mainly minor ICD, and especially in combination with other irritants. A dose-response relation to frequency of handwashing was reported, but no threshold level could be described. The level of evidence is considered strong. Regarding occupational exposure to disinfectants and soap the evidence for a causal association to ICD was moderate, while the evidence for a combined effect to other wet work exposures i.e. combined effect of soap and water was strong. Regarding occlusive glove exposure without concomitant exposure to other irritants the highest quality studies and supplementary evidence from experimental studies supported a limited evidence of a causal association with ICD. Regarding metalworking exposures, the evidence was consistent with a moderate association between metalworking fluids and mainly minor ICD. Regarding ICD, due to mechanical exposures the evidence was scarce and though consistent it did not allow for a firm conclusion why the level of evidence is limited.

Regarding prognosis of ICD there is a high level of evidence for a poor prognosis of complete healing with a high proportion not having complete healing. There is a strong evidence for a better healing prognosis when exposure is ceased through change of occupation or work tasks, however when the outcome was

improvement (healed or better) of ICD the level of evidence in relation to work changes (occupation or work tasks) is limited.
Accounting for atopy was included in our quality assessment of the studies. Atopic disposition is a well-known vulnerability factor for increased susceptibility for ICD. While atopic individuals in most studies were more susceptible to develop ICD, inclusion of atopic dermatitis in adjusted analyses in general did not alter the effect of occupational irritant exposures for risk of contact dermatitis.
The studies did not provide substantial evidence for influence of gender, age or private exposures on development of ICD.
Limitations in the studies included risk misclassification of exposure and outcome. Most study had imprecise exposure assessment as very few included quantitative or semi-quantitative exposure assessments, and relied on self-reported exposures. Outcome of supposed ICD was self-reported in several studies, and outcome definition of ICD varied across studies. Many of the studies were cross-sectional adding to risk of selection and information bias.

Conclusion: The review provides strong evidence for an association between irritant exposures and ICD for wet work, detergents and disinfectants, moderate for metalworking fluids, limited for mechanical and glove exposure and a strong evidence for a poor prognosis of ICD.

4 Abbreviations

ACD: Allergic contact dermatitis

AD: Atopic dermatitis

CD: Contact dermatitis

CS: Cross sectional

CU: Contact urticaria

DNBII: Danish National Board of Industrial Injuries

HCW: Healthcare workers

HE: Hand eczema

ICD: Irritant contact dermatitis

IG: Intervention group

MMMF: Man made mineral fibres

MWF: Metal working fluids

O-MWF: Oil based metal working fluids

OCD: Occupational contact dermatitis

OICD: Occupational irritant contact dermatitis

OSD: Occupational skin disease

OR: Odds ratio

PP: Prevalence proportion

PR: Prevalence ratio

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

QUOROM: Quality of reporting metanalysis

RR: Relative Risk

TEWL: Transepidermal water loss

W-MWF: Water based metal working fluids

5 Background

5.1 Introduction

Irritant contact eczema (in English literature traditionally irritant contact dermatitis- ICD) is a common disease. General population studies have reported incidence of non-specific hand eczema around 5.5 /1000 person-years, point prevalence around 4%, 1 year prevalence around 10% and lifetime prevalence of 15 %, with ICD being the most prevalent type and with the highest frequency of self-reported hand eczema among young women (1). Contact dermatitis (CD), mainly hand eczema (HE), is the most frequently recognized industrial injury in Denmark with up to 2000 annual cases recognised and compensated by the Danish National Board of Industrial Injuries (DNBII), table 1(2). The allergic cases constitute 30 % of the recognised cases of occupational contact dermatitis (OCD). However, the majority of cases, around 70 % are caused by irritant exposures, mainly wet work, but also use of occlusive gloves, exposure to fresh food, detergents, different oils and dirt. The majority, around 70 %, of the recognised cases of occupational ICD (OICD) in Denmark are female and the most frequent profession are healthcare workers, kitchen personnel and cleaning personnel with predominantly exposure to wet work, table 2 (3).

Currently there is a lack of knowledge, and no systematic review regarding the exposures, including the quantity of exposures, sufficient to cause irritant eczema or aggravate pre-existing eczema. Previously only few systematic reviews on occupational ICD (OICD) have been published mainly focusing on treatment and prevention (4-8). Until recently only few epidemiological studies of OICD have been published and most of our knowledge about OICD has been derived from clinical case reports and clinical studies of groups of patients with little contrast in exposure.

5.2 Objectives

On this background, a literature review was requested to create a high-quality, scientific and up-dated reference document of the existing epidemiological evidence for causal relations between occupational exposures to skin irritants in the working environment and ICD.

In this report, we aim to perform a systematic review to present assessment of the risk of ICD in relation to level, severity and duration of the exposure (dose-response relation) to occupational irritants, possible threshold values (lower limit of effect) and prognosis of ICD.

In our assessment, we aim to give a summarized description and estimation of the dose-response and dose-effect correlations, a description of the time of onset of the disease in relation to exposure, a description of the types of work in question, likely causal mechanism and an assessment of the prognosis of ICD as well as the impact of continuous exposure on prognosis.

The reference document aims at reporting the principal exposure dimensions, type of exposures, intensity, frequency and duration and at comparing these with an assessment of the size of the risk and possible threshold values (lower limit values of effect). The reference document will assess 1. the current knowledge on the prognostic significance of continued occupational exposures, 2. prognosis of skin disease before and after the subjects first fulfilled the case criteria and 3. the effect of exposure cessation. The primary prognostic outcomes will be measures of persistence and severity of symptoms and physical findings. Studies on duration of sickness, absence from work and other prognostic outcomes may be included as contributing evidence. It is anticipated that the evidence on these issues will vary widely depending on the occupational setting and exposure (7).

The report aims to account for the significance of possible competitive, pre-existing diseases, non-occupational exposures (i.e. exposure to wet work or other skin irritants in the private environment) and other non-occupational factors (i.e. heredity, atopy, gender, age), for the development of irritative dermatitis and if possible asses a quantitative assessment of the role played by occupational exposure in relation to non-occupational diseases/factors. The description on non-occupational factors will mainly be based on published reviews in the background section, but studies on occupational factors will also be rated according to their ability to account for relevant competing pre-existing conditions.

If the evidence is insufficient to meet these objectives, the limitations of the present knowledge will be outlined and major research needs delineated.

5.3 The outcome of investigation

5.3.1 Definition of ICD and irritant HE

CD has been defined by the European Society of Contact Dermatitis as an eczematous local inflammatory skin reaction caused by direct and usually repeated exposures to harmful objects or chemicals which, depending on point of contact, can occur anywhere on the body. CD is clinically characterized by itching papules or vesicles, but may vary from slight hyperkeratosis (thickening of the outermost layer of the horny layer of the skin), small fissures to extensive redness, swelling and oozing. Histopathological CD is characterized by inflammation in the superficial parts of the skin, i.e. the outermost layers of the dermis with involvement of the epidermis. Healing is without scars. Besides ICD, there are three other forms of CD, with the most important being allergic contact dermatitis (ACD), which is characterized by an acquired hypersensitivity with involvement of "allergen-specific" T cells as mediators of the inflammatory skin reaction (type 4 allergic reaction). Another form of CD is photocontact dermatitis, which is the result of an interaction between a harmful substance in the skin and ultraviolet radiation (UVA light). Photocontact dermatitis can be either a phototoxic reaction involving UVA light and certain photosensitisers i.e. psoralens typically found in different plants causing phytophodermatitis, or may also be a photoallergic reaction. Finally, CD may be because of a type 1 allergic reaction i.e. contact urticaria based on IgE specific antibodies and combinations of these different types of CD (9, 10).

ICD, is the most common variant of CD and ICD has traditionally been defined as a local inflammatory non-specific reaction of the skin, following single or repeated exposures to an irritant, where an irritant has been defined as any agent, psychical or chemical, capable of producing cellular perturbation, if applied for sufficient time and in sufficient concentration without requiring prior sensitization of the immune system (11, 12).

ICD is not a clinical entity, but rather a spectrum of diseases. The spectrum of clinical presentations and etiological factors of ICD is broad and depending on the offending agent, concentration of the irritant on the skin, the type of exposure and the individual response. Clinical entities have been described by some authors to encompass a classification scheme the following 10 phenotypes based on both morphology and mode of onset:

1) Acute ICD, for instance chemical burns are caused by strong irritant agent i.e. strong acids, alkalis, oxidants, reducing agent as well as some elemental metals, which in most cases arise as a result of an occupational accident where irritant reaction reaches peak soon after exposure and afterwards regresses and heal.
2) Delayed acute ICD is a reaction to certain irritants for instance benzalkonium chloride, sodium lauryl sulphate and diacrylates where symptoms are delayed for 8-24 hours but otherwise like acute ICD.
3) Irritant reactions, which encompass cutaneous reactions that do not fulfil the clinical picture of dermatitis, and has been described with monomorf skin changes characterized by either scaling, redness, vesicles, pustules or erosions and associated to exposure to mild irritants i.e. water, soap and detergents.
4) Cumulative (chronic) ICD, the most common presentation, is described as the consequence of multiple subthreshold irritant injuries to the skin, where the time between insults is too short for complete restoration of skin barrier function and is linked to repeated exposures to weaker irritants e.g. wet work. Clinically chronic ICD has been described with symptoms of itching and pain, and signs of dryness, erythema and vesicles and hyperkeratosis, lichenification, chapping and fissuring.
5) Traumatic ICD, caused by acute skin traumas such as burns and lacerations.
6) Acneiform ICD, a result of exposure to irritants like mineral oils, tars, naphthalene and chlorinated aromatic hydrocarbons e.g. chloracne.
7) Non-erythematous ICD, defined as subclinical form of ICD without clinical visible inflammation, detectable only by bioengineering methods.
8) Subjective (sensory) ICD, characterized by lack of clinical signs, but individuals complaining of subjective sensation of stinging and burning after contact with certain chemicals i.e. lactic acid.
9) Friction ICD, characterized as a rarely documented result to low grade friction with erythema, scaling, fissuring and itching around the area of frictional contact.
10) Asteatotic ICD (eczema cracquelé), a variant of ICD seen in mainly on the legs of elderly individuals in the winter and associated to frequent bathing without remoisturizing of the skin (11-13)

Others classify clinical ICD into only four types, with slightly different criteria, i.e.:

1) chemical burns from strong acids or alkalis, including severe skin damage with formation of necrotic scars.
2) irritant reactions/acute irritant reactions, as in the above monomorphic reactions not meeting clinical criteria for "dermatitis" and here specified also to include initial stage of "dryness".
3) Acute ICD, including both the above mentioned acute and delayed acute ICD.
4) Chronic irritant ICD/cumulative insult dermatitis most often localized on the hands (14).

Irritant HE is the major location of ICD and as for CD and ICD in general no gold standard for HE diagnosis or classification of HE exists (15). During the recent years, several suggestions of classification of HE for has been proposed.

One suggestion from the Danish Contact Dermatitis Group (published in 2011) stated HE as a polymorph clinical condition typically with morphological change over time and proposed a subdivision of HE into 6 clinical types based on morphological appearance, i.e.:

1) Chronic fissured HE
2) Recurrent vesicular HE
3) Hyperkeratotic palmar eczema
4) Pulpitis
5) Interdigital eczema
6) Nummular HE

and a further aetiological sub- classification into ACD, ICD, protein contact dermatitis, atopic HE and aetiological unclassifiable HE (16).

Another recent suggestion on classification of HE recommended in a guideline from the European Society of Contact Dermatitis (ESCD) is based on a combination of mainly aetiology and morphological signs and defined seven subgroups of HE, i.e.:

1) ICD
2) ACD
3) Atopic HE
4) Contact urticaria (CU)/protein contact dermatitis
5) Vesicular/pompholyx endogenous HE
6) Hyperkeratopic endogenous HE
7) Unclassified HE

with further combination of diagnoses e.g. ICD with and without atopic HE and combined ICD and ACD. The subgroup of ICD requires a documented exposure of the hands to an irritant being quantitatively likely to cause contact dermatitis, with no relevant contact allergy, while ACD and CU respectively requires relevant exposures to contact allergens identified by patch respectively prick tests, and the diagnosis of atopic HE is made in a patient with medical history of atopic eczema and no documented irritant and/or contact allergen likely to cause the eczema (15, 17, 18).

No specific diagnostic test exists for ICD and as stated above diagnosis is, and has historically, typically been made clinically as an exclusion diagnosis based on no findings of allergic CD and a temporal relationship to an anamnesis of supposed relevant irritant exposures (19).

5.4 The Exposures

Occupational ICD has been described in relation to exposure to various chemicals, soluble oils/metalworking fluids, wet work, detergents, occlusion by gloves, foods, exposure to plants and mechanical friction.

The most prevalent exposure has been reported as wet work in various industries, including healthcare industry, service industry (cleaners, hairdressers), but also as part of exposure to e.g. metalworking fluids.

5.4.1 Definition of wet work

The criteria and definition of wet work are not well defined internationally and has primarily been based on the legal classification set by occupational dermatologist in Germany. The German Approved Code practice TRGS 531, current TRGS 401 (technical rules of hazardous substances), initiated in 1996 define wet work as activities during which workers spend a considerable proportion of their working time in a wet work environment or wear liquid-proof gloves or wash their hands frequently or intensively. They state criteria for presence of wet work as work >2 hours/day with the hands in a wet work environment or frequent or intensive hand washing or wearing gloves with occlusive effect for a corresponding period (20, 21). A definition of frequent or intensive hand washing is not given in the TRGS, but has been suggested in the literature to about 20 times/day (18, 20).

5.5 Descriptive epidemiology of OICD

The majority of studies estimating the incidence of occupational skin diseases (OSD) including OCD and OICD has been based on different occupational disease registers providing national data on notifications of occupational skin diseases based on voluntary or mandatory reporting schemes in which most reported incidences of OCD has varied from 5-19 cases per 10.000 fulltime worker year (20, 22-24). These national registers are usually incomplete as a result of under-reporting of the diseases and registers are often not fully comparable due to differences in reporting practice across countries (20, 22, 24). For in-

stance, an underestimation by 10-50 times due to milder cases not being registered has previously been estimated for reporting of incidence of occupational skin disease in the USA in statistics originating from annual surveys of random sample of employees in the private industry. The extent of underreporting has however been judged to differ among countries, as each has its own notification system (20). In Denmark, underreporting of OCD among hairdressers has recently been estimated in a register-based questionnaire study in which only 21% of hairdressers with HE had their HE reported to the National Board of Industrial Injuries (25). In the United Kingdom (UK) data on OCD are based on a voluntary reporting scheme of the THOR network with dermatologist (EPIDERM) and occupational physicians (OPRA) reporting confirmed or suspected cases of occupational skin disease including the occupation of the patient. In the latest reports of OCD from this scheme from 1996-2001 (table 3) and from 2002-2005, the overall incidence of OCD reported by occupational physicians was substantially higher (around 10 times) than among dermatologist with overall incidences of OCD in the first period of 0.7 and 5.1 and second period of 0.7 and 8.4 per 10.000 worker year respectively (26, 27). The proportion of ICD was similar with 40% among dermatologist reporting to EPIDERM and 36% among occupational physicians reporting to OPRA. The proportion of allergic and mixed/or unspecified dermatitis differed however significantly as ACD was reported in 43% by dermatologist and only 14% by occupational physicians (27). In both periods, the most frequently reported suspected agents were rubber chemicals/latex materials and irritants like soap/cleaners and wet work among dermatologist while other substances like petroleum, solvents and cutting fluids were also prevalent in reports from occupational physicians.

In Germany, Denmark and Finland reporting of OCD is mandatory. In Germany reports have been published from standardized population based registers of OSD established in the Saarland and Northern Bavaria with data collected during 1999 to 2001 and from 1990 to 1999.

The Saarland study reported an overall annual incidence of OSD of 6.8 per 10,000 workers in 16 occupational groups. The study was based on 263 notifications of OSD with confirmed occupational causation, of which 75% of diagnoses included ICD (several diagnoses possible). Annual incidences of OSD per 10,000 workers ranged from 1.5 to 48.2 and were highest among hairdresser (48.2), bakers/pastry cooks (32.7), cooks (18.7), cleaners (13.9) and among nurses (12.6) (28).

The study from Northern Bavaria included 3,097 patients with OSD from 24 occupational groups, with an overall frequency of 57% involving ICD, 41% ICD alone and 15% ICD combined with ACD. The overall annual incidence of ICD per 10,000 workers was 4.5, while the incidence of ACD was 4.1. The highest incidence of ICD as well as ACD per 10,000 workers was reported among hairdressers of 46.9 and 67.2 and among bakers of 23.5 and 10.9. In both groups, a large proportion of patients had both ICD and ACD, 19% and 15% respectively. In table 4 and 5 further details from the study is presented, including the most frequently self-reported exposures in the different occupational groups (29, 30).

Based on recognized notifications of 758 persons with occupational hand eczema from 2001 to 2002 from the DNBII incidences of OCD of the hands and proportions of sub-diagnosis of OICD, occupational allergic contact dermatitis (OACD), occupational contact urticaria (OCU) and combined diagnosed was reported

for different occupational groups in Denmark along with the overall most frequent exposures (31)). The study reported the highest overall annual incidence rates of OCD among bakers and hairdressers of 83.7 and 56.1 per 10,000 workers with ICD contributing in 63% and 74% of cases respectively corresponding to overall annual incidence of ICD of 51.0 and 25.6 per 10,000 workers respectively. The overall most frequent irritant exposures in the study were wet work (water and soap) for females and oils for men (31). Further details on calculated incidences of ICD based on the study is presented in table 4. Also in Denmark incidence rates of ICD as a single diagnosis was reported from a study from 2003-2010 among 1,000 workers in The Capital Region of Denmark diagnosed with severe OCD at a specialized tertiary dermatological clinic department. The rates according to occupation were calculated based on information of employees in the region. The study reported an overall annual incidence of OCD of 1.9 and 1.1 per 10,000 workers in females and males respectively, where 47% and 57% was ICD, corresponding to annual incidences of ICD of 0.9 and 0.6 per 10,000 workers respectively and an overall incidence of 0.8 per 10,000 workers. Incidence of ICD in several occupation groups are comparable to the study in North Bavaria, e.g. 43.0 per 10,000 workers in hairdressers and 25.6 in bakers respectively (32). For further details see table 4 (incidence of ICD calculated from data supplied in the study).

5.6 Individual competitive-, pre-existing diseases and risk factors

While exposure to irritants at work is a necessary condition for development of ICD, risk of OICD may be modified by individual susceptibility through several endogenous individual factors, as well as competing exposures in the home environment.

5.6.1 Atopy, filaggrin mutations and other genetic factors

Atopic disposition, especially a personal history of childhood atopic dermatitis (AD) has been described as a well- known vulnerability factor for increased susceptibility for irritant HE /ICD (11, 33-37). A history of AD has been reported to increase the odds ratio (OR) of developing HE by a factor 3 in wet as well as in dry work (33, 34). The importance of mucosal atopy, i.e. type 1 IgE mediated allergy, is disputed and less predictive, but seems to be a significantly lower risk factor than atopic dermatitis (11, 18). When individuals with atopic disposition including AD are exposed to irritants one may ask whether HE is due to atopy or a manifestation of ICD, i.e. whether irritants precipitate or aggravate HE in individuals with a history of AD. As discussed by Coenraads et al in epidemiological terms it is more logical to look at AD as an effect modifier, i.e., as a vulnerability factor, asking to what extent the presence of AD elicits more hand eczema from occupational exposure to irritants, which the above mentioned equal multiplicative increase of risk due to atopy among exposed and non-exposed supports (33, 34). One must realize that, while individuals with atopic disposition may have a higher risk of HE at a given exposure, not all with atopy exposed to irritants develop HE. This is shown by a Swedish study where 25% with atopy in high risk occupations as hairdressers and nursing assistants did not develop HE (35).

In recent years genetic factors other than atopy and combinations of these genetic factors with atopy have emerged as possible factors that may contribute to increased susceptibility of HE. These factors include variations/polymorphisms of genes involved in the skin barrier function and inflammatory mediators including different cytokines and especially polymorphism of gene coding for the epidermal protein filaggrin which, as a structural protein in the epidermis, is important for the formation of the epidermal skin barrier (18, 38-43). Filaggrin gene loss-of-function mutations have been identified as a strong risk factor for AD (18, 39) and, as a case control study reported, for an increased frequency with an OR of 2 for filaggrin gene loss of function mutations in relation to chronic ICD along with a higher prevalence of flexural eczema and a higher atopy score for carriers of the mutations (43). Thus, the question has been whether the association to ICD is an independent vulnerability factor or only exerts its effect on ICD through AD (39)? Recently another case control study among German patients with OICD reported an OR for filaggrin mutations adjusted for AD of 1.62, while a Dutch follow-up study of apprentice nurses showed no increased risk of HE conferred by filaggrin mutations but only a higher risk when concomitant AD (40, 41). Studies have also reported a risk of healthy worker effect with carriers of filaggrin gene mutations avoiding professional exposure to irritants as well as worse prognosis of ICD among carriers of filaggrin loss-of-function mutations in combination with atopy (44, 45).

5.6.2 Previous Hand Eczema

Previous episodes and early onset of HE are also well known risk factors for development of HE, including ICD. This probably relates to individuals with increased susceptibility due to inborn characteristic of the skin, including atopic skin disease, but also possibly due to behavioural patterns regarding for instance habits of skin protection and hand washing with increased risk of barrier impairment (18, 46, 47).

5.6.3 Sex

ICD including OICD is almost consistently reported more frequently in women, especially among young women. However, no sex difference of irritant reactivity has been confirmed in experimental studies, and as many female-dominated occupations involve more extensive wet work along with females especially young females being more likely to spend time with wet work at home, the difference between male and females is suspected to be due to differences in especially occupational but also non-occupational exposures to irritants, especially among young women with small children (1, 11, 48). This is supported by the observation that caring for children under the age of four and lacking a dish washing machine significantly increased the risk of contracting hand eczema in a population of female hospital workers (49).

5.6.4 Age

Skin susceptibility to irritation decreases with increasing age. Population studies on hand eczema has consistently shown a trend of declining frequency with age, especially among women, where self-

reported rates of hand eczema were highest among women in their twenties. Findings among males has been less consistent, but a decreasing trend has also been reported in several studies (1, 11, 50).

5.6.5 Smoking

The relation between smoking and HE has recently been evaluated in a review including 20 epidemiological studies of which seven were from occupational settings. The review concluded that smoking may cause an increased frequency of HE, particularly in high risk occupations, but described conflicting, inconsistent results since approximately half the studies showed an increased prevalence and/or severity of HE in smokers, while the other half reported no association, though a protective effect of smoking was only reported in one study (51).

5.6.6 Non-occupational exposures to irritants

Exposure to irritants in the home environment may be of relevance for the development of ICD and the subgroup of OICD and it has, as mentioned previously, been speculated whether the increased frequency of ICD reported in women compared to males can be explained by differences in domestic chores i.e. minding of young children, dishwashing and cleaning (1, 40, 52, 53).

5.7 Background Tables

5.7.1 Table 1

table 1	Recognized cases of occupational ICD and ACD (eczema), Danish National Industry Injuries Register 2011-2015 among approximately 2.7 million in the working population (2, 54)						
		2011	2012	2013	2014	2015	2011-2015
ICD	All	962	1267	1274	752	1168	5423
	% females	73	68	68	66	69	69
ACD	All	387	449	388	264	434	1922
	% females	64	60	57	55	65	61

5.7.2 Table 2

Table 2.	Most frequent occupations and exposures, based Danish National Industry Injuries Register 1,504 recognized cases OCD Denmark 2010 (3)

Most frequent occupations ICD	ICD-all	ICD-all	ICD-only	Wet work†	Other frequent reported exposures
	n	% of OCD		% of all workers with ICD in occupational group	
Healthcare workers	334	86	78	96	Gloves*: 4; disinfectants: 0.9
Kitchen personnel	148	83	77	99	Foods: 57
Cleaning personnel	108	92	85	90	Gloves*: 10
Craftsmen incl. building industry	81	72	66	28	Oil: 30; cement/concrete: 14, mechanical: 10
Hairdressers	81	80	54	99	
Nursery teachers	65	96	88	96	
Mechanics/fitters/technicians	57	81	68	18	Oil: 68; solvents: 7; gloves*: 7
Factory workers	45	51	42	38	Oil:13; gloves*: 9; mechanical: 9; cold/warm: 9
Machine operators/ metalworkers	45	80	59	27	Oil: 67; several 2-4% (n: 1-2)
Sales assistants	35	85	73	62	Foods: 17; Mechanical:11; paper /cardboard:11
Bakers / confectioners	27	66	56	92	Foods:78;
Dental assistants	33	85	62	94	
Laboratory personnel	21	84	80	67	Gloves*: 29; Disinfection*: 10
Butchers/slaughterhouse workers	20	86	70	60	Foods: 30; gloves: 22
Total	1209	80	70	75	Foods: 9; oil: 7; gloves: 4; mechanical: 3

†: Wet work included frequent hand washing, use of water and soap and/or gloves. * Not accompanied by wet work

ICD only: Single diagnose of ICD; ICD-all: Single diagnose of ICD + combined diagnoses including ICD.

5.7.3 Table 3

Table 3. Incidence OCD and most frequent agents registers in the UK– reporting schemes dermatologist and Occupational Physicians 1996-2001 (55)

	Per 10.000 workers pr. year				Most frequent agents %	
	Dermato-logists		Occupational physicians		Dermatologists	Occupational physicians
	1					
Industrial Category	Rate	n	Rate	n		
1. Agriculture, for-estry &fishing	1.2	50	3.7	1	Rubber chemicals: 16 Colophony: 10	-
2. Mining & quarry-ing	1.2	12	13.7	20	-	Cement/plaster/masonry: 40 Other agents: 30
3. Food & organic material manufac-turing	1.0	152	5.7	86	Foods/flour: 17 Rubber chemicals:11 Wet work: 9	Petroleum products: 12 Nickel: 12 Resin/acrylics: 9
4. Petrochemical, rubber & plastic manufacturing	1.5	128	18.4	299	Resins/acrylics: 16 Solvents & alcohol: 13 Rubber chemicals:10	Resin/acrylics:10 Wet work: 9 Solvents /Alcohols: 8
5. Metallic & auto-motive product manufacturing	1.4	354	36.9	536	Cutting oils/coolants: 19 Resin/acrylics: 18 Petroleum products: 12	Cutting oils/coolants: 15 Soap/cleaners: 14 Resin/acrylics: 13
6. Utilities & con-struction	0.7	152	2.5	39	Chromium/chromates: 29 Cement/plaster/ masonry: 21 Resins/acrylics: 14	Wet work:21 Nickel: 21 Solvents/alcohol: 21
7. Health & social services	1.1	325	3.4	440	Rubber chemicals: 34 Wet work: 27 Soap/cleaners: 15	Rubber chemicals:46 Soap/cleaners:18 Wet work:15
8. Others	0.4	749	51	148	Wet work: 19 Soap/cleaners: 18 Nickel: 15	Soap/cleaners: 46 Rubber chemicals: 16 Resin/acrylics: 12
Overall	0.74	2039	5.1	1639	Rubber chemicals: 16 **Wet work**: 13 **Soap/Cleaners**: 12 Nickel: 10 Resin/acrylics: 7 Foods /flour: 6	Rubber chemicals: 17 **Soap/Cleaners**: 14 **Wet work**: 8 Resin/acrylics: 7 **Petroleum products**: 7 **Cutting Oils/coolants**: 6

Selected results from (55), table 1, 5 and 6. Study included 2039 cases of OCD reported by dermatologist and 1639 cases reported by occupational physicians.

5.7.4 Table 4

Table 4. Yearly incidence OICD /10.000 workers 3 studies –Germany (Northern Bavaria) and Denmark, 2 registers of recognized OCD and one regional patient-register of OCD (selected results) (29, 31, 32)

	Germany 1990-99†	Denmark, national 2001-02¶ OHE		Denmark, Capital region 2003-2010*
	ICD-all	ICD-only	ICD-all	ICD-only
	n=1760	n=388	n=461	n=509
Wet work occupations				
Hairdressers	46.9	17.6	25.6	43.0[a]
Cleaners /housekeepers	2.4	4.6	5.4	3.2
Dental surgery assistants /dental technicians	4.8	20.9	25.1	5.7[a]
Healthcare workers	4.0	4.5	5.3	-
Nurses and nursing assistants	-	-	-	1.7
Food occupations				
Bakers	23.5	39.4	51.7	25.6
Pastry Cooks	16.9	-	-	-
Cooks	5.4	-	-	12.0
Kitchen workers	-	-	-	1.4
Kitchen workers/ cooks	-	22.9	28.5	-
Others				
Assemblers / Manual workers	3.1	-	-	1.0[b]
Florists	7.8	-	-	-
Title setters & terrazzo workers/ Bricklayers	8.1	-	-	4.2[b]
Painters (& varnishes)	4.1	-	-	6.1
Machinists / Machine operators	5.9	-	-	7.2
Mechanics	4.2	-	-	12.3[b]
Metal processors	3.6	-	-	
Metal surface processors	6.4	-	-	
Blacksmiths	-	-	-	3.4[b]
24 occupational groups overall /total	4.5	-	-	0.6

†(29) Study included 3097 patients with OSD in 24 occupational groups, ~59% of all patients in register of OSD in Northern Bavaria, Germany 1990-1999. Total 41% ICD, 36% ACD, 16% ICD+ACD, 7 % other patients. 61% females.

¶(31)Study included 758 patients with recognized OCD hands (OHE) from Danish National Industrial Injuries Register 2001-2002. 62% ICD, 26% ACD or CU; 12.2% ICD+ACD or ICD+CU. 64% were females.

*(32)Study included 509 cases of ICD among 1000 cases of severe OCD (62% females), 88% HE from register of Dermatological Department covering capital region Denmark 2003-2010. Study coded 64 cases of both ACD and ICD as ACD. Study reported incidence figures separately for females and males. Combined incidence presented here by calculations based on information from original article

ICD only: Single diagnose of ICD; ICD-all: Single diagnose of ICD + combined diagnoses including ICD.
a) females; b) males.

5.7.5 Table 5

Table 5 Register Germany (Northern Bavaria) occupational skin disease (OSD), most frequent self-reported skin contact substances or chemicals skin contact among 2128 workers with OSD in 24 occupational groups (selected results) (29)					
	Deter-gents %	Disin-fectant %	Chemi cal* %	Cut ting %	Others %
Wet work occupations					
Hairdressers	55		55		adhesive¶ 10
Cleaners /housekeepers	87	49	8		solvents: 6; dust 5
Dental technicians	44	22	22		dust 61
Healthcare workers	72	76	13		Solvents: 9; dust: 6
Food occupations					
Bakers	44	5	21		Dust: 18
Pastry Cooks	74	15			-
Cooks	82	29	6		-
Others					
Assemblers	44	3	13	31	Dust: 19
Title setters /terrazzo	23	10			building†: 87; dust: 65; adhesive¶: 45
Painters (& varnishes)	44	8	26	12	adhesive¶: 62; solvents: 58; dust: 28; building†:20
Machinists	31	6		54	solvents: 58; dust: 37;
Mechanics	38	0	15	73	dust 58; solvents: 35
Metal Processors	42	4	15	48	dust: 29; building†: 7;
Metal surface processors	18	2	12	65	dust: 37; building†: 5
24 occupational groups overall /total	52	24	24	17	dust: 18; solvents: 12; adhesive¶: 12; building†: 9

(29), table II, selected results from 14 of 24 reported occupational groups, only reported when at least 5 reports of exposure in occupational group.
Chemical*: chemical (acid and alkaline); Cutting±: cutting fluids, mineral oils, lubricants; adhesive¶: Adhesive, varnish, paint; building†: building materials (cement, concrete etc.)

6 Material and methods

6.1 Literature search

The systematic review is based on PRISMA (56) (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) that are a revision of the QUOROM (quality of reporting metanalysis) (57).

The literature search was performed in the following international databases: The National Library of Medicine (PubMed), Embase, web-of science and OSH-update, the later including the following specialized databases on occupational safety and health: HSELINE, NIOSHTIC, CISDOC and RILOSH. The literature search was performed based on the search terms shown in supplementary.

We included papers with abstracts published in English, Danish and German from 1980 and onward. However only articles in English and German were eligible based on inclusion and exclusion criteria and passed the selection of studies. The search results were imported into databases and duplicates were subsequently removed. One member of our group performed the initial title screening of articles.

In further screening of abstracts and articles each paper was reviewed independently by two members of the group. The two reviewers had to agree before a paper was included for data extraction to systematic review.

6.2 Inclusion criteria

Preselection of articles on associations between irritant exposures and ICD was based on the following eligibility criteria:

1. Original epidemiologic peer-reviewed studies on occupational exposure to irritants and outcome of ICD.
2. Study design included case-control, cross-sectional and follow-up studies but excluded case studies, case series i.e. patient populations reporting on proportion of ICD and ACD, meta-analyses and reviews.
3. The included studies had to provide qualitative or quantitative exposure contrast to presumed irritant exposures, that is contrast either within the exposed group e.g. high and low exposure or by including a control group without exposure. Studies on exposure–disease relation without exposure contrast, e.g. studies solely reporting prevalence or incidence of ICD in different occupational groups without providing information on the amount of exposure, was excluded.
4. For outcome of ICD, we included studies which reported ICD or irritant changes resembling mild cases and association to irritant exposures. We included studies with clinical assessment including patch test, which were able clearly to distinguish between ICD and alternative diagnoses, i.e.

ACD, but also studies with less diagnostic accuracy, i.e. studies with clinical examinations but no patch tests, and studies based on self-reported outcome of mainly HE, if the studied association was to presumed irritant work exposures.

5. Studies with main focus on atopic dermatitis, ACD and CU, without indication of ICD or exposure to irritants, were excluded.
6. For studies on prognostic factors of ICD, we only included follow-up studies of cohorts with clinically verified occupational ICD. Studies with sole focus on treatment or prevention e.g. use of barrier creams were also excluded.

6.3 Data assessment: extraction, quality, bias and confounding

From each study, we extracted core information relevant for description of relations between occupational exposures and diagnosis or symptoms of ICD, individual risk factors and prognosis of ICD and for assessment of internal validity (selection bias, confounding, information bias) and overall quality of study into data evaluation sheets. One reviewer extracted the information, which was subsequently evaluated by a second reviewer and disagreements were solved by discussion.

We systematically assessed all studies for eight quality dimensions resembling risk of bias and confounding, previously used in another systematic review to the Danish Work Environment Fund(58). Quality factors were related to:

1) study design (3 parameters)
2) exposure assessment (2 parameters)
3) outcome (2 parameters) and
4) confounding (1 parameter)

Quality factors were dichotomized in each study on high and or low quality/risk given score of 0 (low quality/high risk) or 1 (high quality/low risk) according to the following criteria:

I. study design: cohort study or case control study with population or hospital control vs. case control studies with convenience controls and cross-sectional studies
II. size of study, number of participants: 75 cases vs. <75 cases
III. response rate >60% vs. <60% (in cohort studies defined as proportion of baseline participating at follow-up)
IV. source of exposure information: non-self-reports vs. self- reports
V. exposure measure: quantitative or semi-quantitative vs. qualitative
VI. source of diagnosis: hospital vs. surveillance schemes, questionnaire or not well-defined sources
VII. diagnosis: well defined diagnostic criteria for ICD vs. other criteria
VIII. possible confounding: accounted for age, sex, atopy in adjusted analyses or by matching vs. no account for age, sex and atopy

In addition, we evaluated the information from the individual studies as high, medium and low quality regarding association between exposure and outcome based on a combination of the above measures and an overall assessment of the paper with main focus on study design, assessment of diagnoses, assessment of exposures and ability to account or adjust for confounders especially atopy.

Core information on study design, population, exposures, diagnoses, study results and quality assessments were subsequently tabulated.

When the study did not provide any kind of risk estimate, the authors of this review calculated prevalence ratios (PR), relative risk (RR) or the OR based on the available data – whenever feasible.

The overall level of evidence of a causal association between an exposure to a specific risk factor and a specific outcome was evaluated based on a classification system established by The Scientific Committee of the Danish Society of Occupational and Environmental Medicine (DASAM), which has been used in other recent reviews (59-61).

The following categories were used:

+++	strong evidence of a causal association
++	moderate evidence of a causal association
+	limited evidence of a causal association
0	insufficient evidence of a causal association or evidence suggesting lack of a causal association
-	evidence suggesting lack of causal association

For further see appendix.

For studies publishing multiple articles on the same issue we decided to include the papers, when it provided additional information of the relation between exposure and OICD.

7 Results

7.1 Selection of papers

The literature search resulted in a total of 1,373 articles. 859 papers originated from PubMed, 218 from Embase, 189 from OSH-update and 107 from Web of Science. Based on the title 850 articles were excluded and 37 articles without an abstract. The remaining 486 articles were evaluated based on the abstract and of those 302 articles were excluded and one article could not be assessed. 183 articles were evaluated by reading of full text articles and finally 48 articles on 43 studies were regarded as suitable for data extraction. In addition, 2 snowball articles were included based on references in included articles and reviews.

7.1.1 Fig. 1 Results from database search

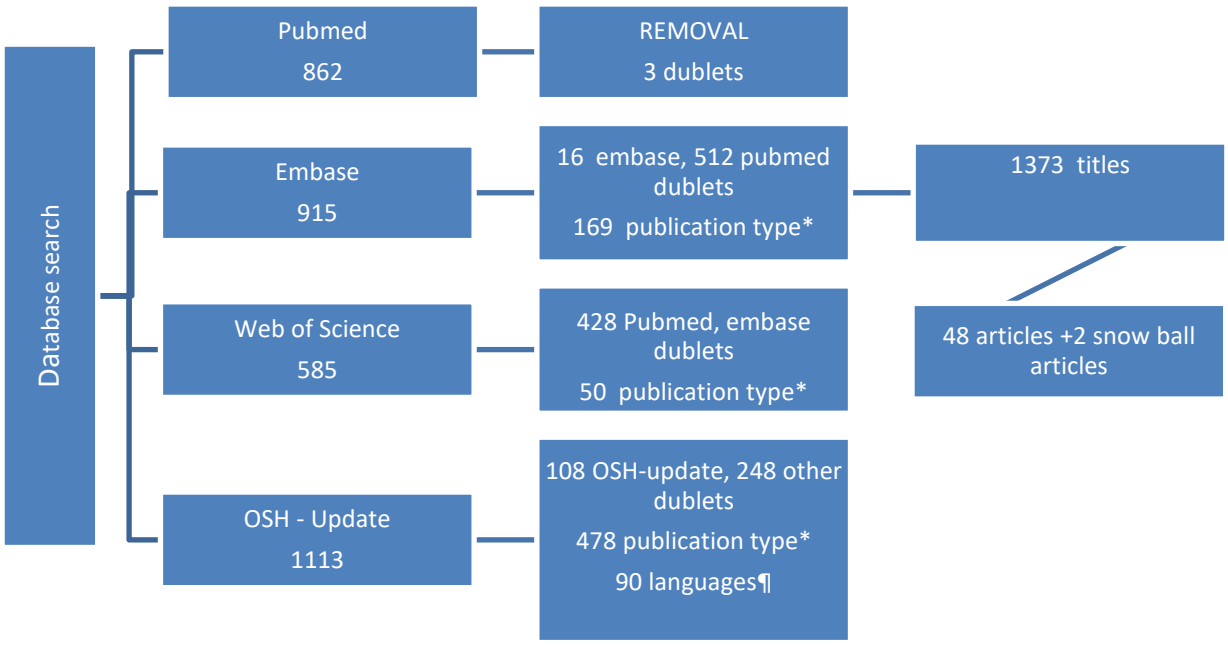
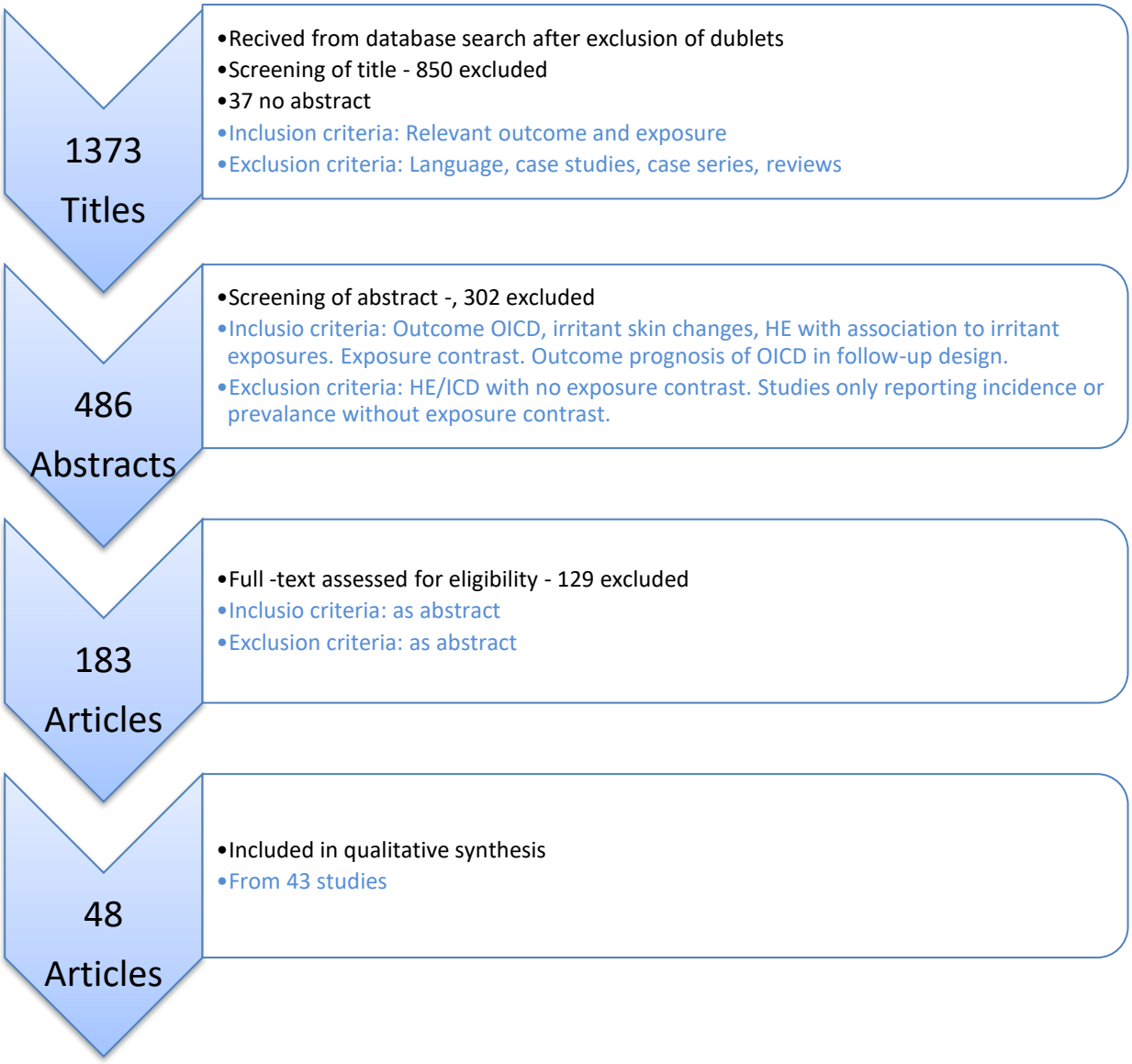


Figure 1: Database search and removal of papers due to identification of duplicates, *conference abstracts, case reports and ¶ papers not published in English, German or Danish.

7.1.2 Fig. 2 Inclusion and exclusion of articles found by the systematic database search



7.1.3 Overall study characteristics

Table 6 to 9 summarize the characteristics and main results of 50 epidemiological papers from 45 studies on occupational risk factors for ICD or irritant skin changes resembling ICD (table 6-8), and studies on prognostic of ICD (table 9). For diagnostic outcome, a clinical diagnosis with patch testing allowing to distinguish ICD from ACD and other diagnoses was regarded the gold standard and was measured in 11 studies shown in table 6 (62-72), 13 papers on 9 studies relying on clinical diagnosis without patch test in table 7 (73-85) and 15 papers on 14 studies relying on self-reported outcome in table 8 (40, 47, 53, 86-97). Table 9 presents characteristics on 12 studies involving prognosis of ICD (96, 98-108). Table 10 presents summary of the quality assessment of the selected papers.

Studies were conducted Norway (67), Sweden (72), Switzerland (76), Poland (63), Spain (97), Austria (99), Australia (100), Israel (90), two studies from Finland (102, 103), two from Italy (66, 70), two from the USA (85, 86), two from Korea (91, 94), three from the UK (98, 101, 105), three from Singapore (62, 75, 104), four from Taiwan (64, 69, 73, 93), four from The Netherlands (40, 65, 80, 95, 106), five from Germany (68, 74, 77-79, 81-84), nine from Denmark (47, 53, 71, 87, 88, 92, 96, 107, 108) and one multicentre European study(89). Studies and were published between 1983 and 2015. One paper was in German (99), the remaining in English.

7.2 Wet work exposure

7.2.1 Design

Wet work has been reported in several work populations, alone or in combination with other irritants or potential allergenic exposures. The main occupations recording wet work exposure in this review are in studies conducted among healthcare workers, in food-related industry and among cleaners.

Exposure to wet work in this review was reported in 20 papers from 15 epidemiological studies (40, 47, 53, 62, 69, 78, 80-85, 90-96) published between 1994 and 2014, 14 industry-based and one population study (47), five follow-up studies and ten cross-sectional studies.

Six studies (seven papers) included healthcare workers (HCW): two follow-up studies, one follow-up with outcome based on clinical assessment without patch test (85), while in one follow-up study (40, 95) and four cross- sectional studies outcome was questionnaire based relying on self-reported symptoms (53, 92-94).

Three studies reported on hairdressers: one follow-up study on hairdressing apprentices reported in four papers with clinical assessment of outcome without patch test (78, 79, 81, 82), one cross-sectional study including clinical assessment with patch test (69) and one cross-sectional study relying on self-reported outcome (91).

Two studies were performed in the food-industry: both included clinical assessment, in one cross-sectional study including patch test (62), while no patch test was performed in one follow-up study reported in two papers at one year and three year follow-up (83, 84).

One cross-sectional study in the rubber manufacturing industry included clinical assessment of outcome without patch test (80), two cross-sectional study on cleaners (96) and hydrotherapist (90) respectively and one follow-up study on young adults from the general population all relied on self-reported outcome (47).

7.2.2 Exposure source and measure

Only one recent study by Lan et al (93) on a subpopulation of non-atopic nurses in a cross-sectional study applied quantitative measurements of wet work exposure by observation, along with measurements of exposure to disinfectants and glove use. In addition, one follow-up study by Visser el al (40, 95) on apprentice nurses by use of diary cards every 2-4 weeks along with symptoms provided semi-quantitative measurements on self-reported wet work activities including hand washing, use of alcohol rubs, glove wearing and other contact with water, soap and disinfectants.

The remaining studies relied on self-reported information on exposures in questionnaire (53, 78, 85, 91, 94, 96) and/or interviews (62, 69, 80, 83, 84, 90) with information given on main wet work task (62,

91), daily (78) or weekly (69) duration of work task (69, 78), duration of wet work (47), frequency of work tasks, frequency of daily hand washing (47, 53, 62, 80, 85, 92, 94) or proportion of wet work (96).

Some of the studies included other exposure variables of relevance for ICD and wet work than reported above, such as fruit preparation and cleansing (83, 84), contact with detergent (62), use of industrial surfactant (80), use of disinfectants (71, 92), and in a number of studies use of gloves, which may be a part of wet work, but will be treated separately in this review.

7.2.3 Outcome

Diagnosis of outcome was clinically assessed in six studies, including patch test in two studies, one among hairdressers with patch testing of most of the participants, while one study in the food industry only performed patch test and prick test when allergy was suspected (62).

All six clinical studies provided some information on criteria for diagnosis or grading of diagnosis, typically in mild or minor dermatitis and moderate and severe or major dermatitis with irritant reactions representing mild cases, typically described as slight erythema, chapping and scaling, without morphology of papules vesicles or fissures (69, 80, 85). One study in the food industry defined OICD as a rash after start of work with exposure to known irritant, improvement away from work and no contact with known allergens (62). One study on hairdressers including patch test with grading of HE in mild, moderate and severe also classified HE per morphology based on evaluation of photographs into an "MP type" described as dry irritant dermatitis of the metacarpophalangeal (MP) areas, and eczematous dermatitis usually of the fingers, and described low sensitivity rate among hairdressers with MP type as opposed to hairdressers with eczema of the fingers (69). One large follow-up study on hairdresser apprentices used an operational definition on any skin changes graded as mild, moderate and severe based on morphology and severity, and the diagnosis of HE required at least one site with moderate severity (78).

In three of the studies without clinical diagnosis outcome relied on self-reported dermal symptoms resembling HE, typically including redness, swelling, cracking, itching and vesicles and in one study of hydrothe-rapists symptoms affecting other body parts (90, 93, 94, 96). In one follow-up study on apprentice nurses skin symptoms were recorded on diary cards every 2-4 weeks (40, 95), one study provided information on use of an algorithm of symptoms from a validated questionnaire (93) with a high specificity and sensitivity (109); and in one study on nurses the questionnaire was supplemented by patch test on a sub-cohort revealing a high proportion of sensitisation (94). Three studies used self-reported HE based on the same standardized questionnaire (47, 53, 92) (NOSQ 2002(110)).

Outcome was reported as incidence/incident cases in five studies (79, 84, 85, 90, 95) and/or point prevalence (current outcome) in eight studies (40, 69, 80, 81, 83, 85, 91, 95) and prevalence during the last year in four studies (47, 53, 62, 92, 94, 96) and in one study non-specified prevalence (93).

7.2.4 Confounding

All but two studies (53, 91) provided information on atopy and multivariate adjusted analyses including atopy, sex and age, along with other occupational risk factors were performed in 8 studies (40, 47, 62, 80-82, 84, 85, 94). In one study, which adjusted for atopy, selective inclusion of hairdressing cohort of non-atopic and selective dropouts of atopic was reported (82), while another study among healthcare workers reported a selective inclusion of workers with atopy (95). Most studies reported an association between ICD and atopy (47, 82, 84, 93), while one study among hairdressers reported no association between HE and atopy (69).

7.2.5 Quality of the studies

All the included studies could potentially be affected by bias or confounding. Nine were cross-sectional studies, and as exposure and outcome is collected simultaneously these studies can only suggest causation; in some cases, causation may even be reversed. However, reverse causation in relation to wet work is unlikely. Selection bias due to healthy worker effect due to selection of diseased subjects out of the exposed cohorts is more likely and may attenuate the results of these studies with probable direction of bias toward unity. This is also the case if more susceptible individuals, i.e. individuals with atopic skin diathesis are less likely to be exposed due to pre-work self-selection and this is not adjusted for in analyses of results.

In the study by Uter el al (81) hairdressing apprentices were less atopic at baseline than office reference workers and more atopic apprentices dropped out of training during the 3-year follow-up pointing toward selection being an important factor that could attenuate effects of exposure. However, in some cases selective participation or dropout of exposed workers with HE may cause an overestimation of effect which cannot be ruled out (96).

As most of the studies relied on qualitative exposure assessment with self-reported exposure it is also probable that exposure misclassification is present, most likely non-differential misclassification causing dilution of exposure contrast, and are therefore also most likely to cause attenuation of results.

In addition, studies may have been affected by misclassification of outcome, least likely for the two studies in which diagnosis of ICD was based on clinical assessments including patch test, most likely for questionnaire based outcome. This concern especially symptom-based outcome where studies have reported low specificity which will tend to create a higher proportion of participants with symptoms, but when non-differential in most cases will cause bias toward the null.

It is not possible surely to distinguish between ACD and ICD without including patch tests, but exposure to wet work must mainly be regarded as a likely irritant especially for exposure of the hands to hand washing, even though allergens in soaps and detergents cannot be ruled out in all cases.

Taken together all the studies had flaws of minor or major character and no studies were regarded as high quality. Two studies were regarded as medium-high quality (81, 82, 85, 93), five studies of low quality (53, 90-92, 96) and the remaining eight studies of medium quality (40, 47, 62, 68, 69, 80, 83, 84, 95).

7.2.6 Results

A meta-analysis could not be performed due to differences in the reported outcomes.

Overall the studies across industries consistently pointed toward a moderate association between wet water exposure, especially frequency of exposure and probable ICD and irritant changes which may also be relevant in the pathogenesis of allergic contact dermatitis and in worsening of pre-existing skin disease.

A dose-response-relation between ICD or HE and hand washing frequency is indicated in three studies (53, 85, 94) and in one study in combination with use of industrial surfactant (80).

Callahan et al in a recent six-month follow-up study in the USA reported a dose-response-relation both for adjusted point-prevalence rate and incidence rate on approximately 1.04, along with significance for hand washing ≥10 times/day of 1.88 and 2.95 respectively (85). The study included clinical diagnosis and patch test with relevant adjustment for confounders and result were despite a relatively small study of healthcare workers all selected to be exposed to hand washing at least eight times per day.

A cross-sectional study by Ibler et al (53) on Danish healthcare workers reported an increase of HE across five categories of hand washing until >20 hand washes, where a significant trend indicating a dose-response-relation has been calculated for this review (53).

Lee et al in a study of Korean nurses, likewise in multivariate analyses, reported a uniform increase in OR for self-reported HE across four handwashing categories with a reference of <10 hand daily hand washes, significant for the categories above 20 times/day, with OR 5.8 and 13.1 for 20-30 times/day and >30 times/day respectively (94).

Vermeulen et al in a study of rubber manufacturing workers reported adjusted OR of minor dermatitis significantly increased for hand washing 5-10 times/day to 3.1, but not for >10 times/day, though the latter also gave an OR above unity on 2.3, but when combined with use of industrial surfactant OR increased to 4.3 and 6.4 both significant and indicating a dose-response-relation (80).

Several studies have reported increased prevalence ratios (PR) or OR for dichotomized hand washing frequencies, Lan et al on exposure to hand washing >6 times/4-hour shift reported adjusted OR 3.0 (93); Visser et al on handwashing_≥8 times per day, adjusted OR 2.2.

Uter el al did not report hand washing >10 times per day significantly associated to HE in hairdressing apprentices, and for hand washing >20 times per day variable results have been reported, with OR in 3 studies ranging from 1.2 to 3.0 (62, 83, 84, 92) significant in two studies (62, 92).

Duration of daily wet work has less consistently been associated to ICD. Uter el al in a follow-up study of German hairdressing apprentices in adjusted analyses reported especially unprotected wet work >2 hours per day significantly associated to HE with OR increasing from 1.6 when using gloves to 1.8 without gloves (81). Guo et al in another study of hairdressers from Taiwan reported time per week shampooing associated to dry MP-type dermatitis, more frequent among apprentice hairdressers but did not provide statistics to support this (69).

Bauer et al in a follow-up study of food industry apprentices reported significantly increased risk of mainly ICD at one year follow-up related to tasks of cleansing >1 hour/day with a relative risk of 1.7, but at three year follow-up only reported a trend toward an increased risk with OR of 1.2 (0.99-1.99) for wet work in general (cleansing and dough preparation up to 4 hours per day)(83, 84).

Nielsen et al in a study of cleaners reported a dose response relationship between hours of weekly wet work and prevalence of self-reported symptoms of HE (96).

Mortz et al in a follow-up study of young adults reported wet work, defined as exposure to wet work or occlusive gloves >2 hours per day or handwashing >20 times per day associated to prevalence of HE (47), and Lazarov et al among hydrotherapists reported >10,000 cumulative hours of pool work associated to CD (47, 90).

In contrast among healthcare workers Lan et al in an observational study of exposure and Ibler et al reported no association of HE to duration of duration of daily hand washing (53, 93).

7.2.7 Conclusion

The available evidence from epidemiological studies support an association between wet work, especially frequent wet work and mainly minor ICD especially in combination with other irritants. No threshold level can be described. The level of evidence is considered strong (+++).

7.3 Exposure to disinfectants and detergents/soaps

7.3.1 Design

Exposure to different disinfectants and soaps/detergents may by itself be important irritants, though these exposures are often reported together with wet work and therefore the effect may be difficult to evaluate.

Exposure to "disinfectants" (53, 70, 71, 92, 95) or/and detergents (62, 69, 70, 80, 91, 95) in this review was reported separately in nine papers from nine epidemiological studies published between 1994 and 2014, all industry-based, two follow-up studies and seven cross-sectional studies.

Five studies were performed among healthcare workers. Two were follow-up studies (71, 95), one based on clinical assessment including patch test and reporting on disinfectants (71), the other on self-reported symptoms reporting on disinfectants and soaps (95). Three were cross-sectional studies, where diagnosis in one reporting on disinfectants and detergents/soaps was based on clinical assessment including patch-test (70), while the others both reporting on use of disinfectants and relied on self-reported outcome of HE (53, 92). Two cross-sectional studies were performed on hairdressers reporting on shampooing of hair, one with full clinical assessment (69), the other with diagnosis based on self-reports (91).

Finally, two cross-sectional studies reported on detergents among workers in the food industry (62) and on surfactants/detergents among workers at rubber manufacturing companies (80) respectively.

Size of the studies varied from 61 to 2269 exposed (53, 71).

7.3.2 Exposure source and measure

Exposure to soap and disinfectants along with other wet work was assessed semi-quantitatively by diary cards every 2-4 weeks in one follow-up study among apprentice nurses (95), while the remaining studies relied on self-reported information on exposures.

7.3.3 Outcome

Diagnosis of outcome was clinically assessed in five studies (62, 69-71, 80), including patch test in four studies, on most participants in two studies (69, 71) and when symptoms in two studies (62, 70). All five clinical studies provided some criteria for diagnosis or grading of diagnosis, e.g. ICD based on clinical history and exposures (62, 70), classification in mild/minor dermatitis and moderate/severe dermatitis with irritant reactions representing mild cases (80), morphological type dry irritant MP type (69) or scoring system for extend of HE/skin irritation (71).

In two studies diagnosis relied on self-reported dermal symptoms resembling HE (91, 95), in one study among apprentice nurses by recording on diary cards every 2-4 weeks (95), while two studies used self-reported HE based on the same standardized questionnaire (53, 92, 110).

Outcome were reported as incidence/incident cases in two studies (71, 95), point prevalence in three studies (69, 70, 80) and prevalence during the last year in four studies (53, 62, 91, 92).

7.3.4 Confounding

All but two studies (53, 91) provided information on atopy, sex and age, however adjusted analyses including these especially atopy was only reported in three studies (62, 71, 80).

7.3.5 Quality of the studies

All the included studies could potentially be affected by bias or confounding. Seven were cross-sectional studies and therefore less suitable to establish causation and prone to information as well as selection bias due to healthy worker selection as discussed in the section about wet work. As most of the studies relied on qualitative exposure assessment with self-reported exposure it is also probable that exposure misclassification is present, most likely non-differential misclassification causing dilution of exposure contrast and therefore this misclassification is most likely to cause attenuation of results. Studies may have been affected by misclassification of outcome, most likely in studies where outcome is based on self-reported disease or symptoms, which as discussed in the section on wet work will tend to cause bias toward no effect of exposure. Taken together all the studies had flaws of minor or major character and no studies were regarded as high quality. Five studies was regarded of medium quality (62, 69, 71, 80, 95) and four of low quality (53, 70, 91, 92).

7.3.6 Results

A meta-analysis was not performed due to differences in the reported outcome.

Overall the studies across industries pointed toward a low to moderate effect on irritant eczema for disinfectants as well as detergents/soaps.

Vermeulen et al in adjusted analyses reported a non-significant association with OR of 1.9 between minor dermatitis and the use of industrial surfactant and irritant skin changes/minor dermatitis in a study of medium quality in the rubber manufacturing industry. Further, a dose response relation was reported between the prevalence of minor dermatitis and frequency of handwashing with use of industrial surfactant with OR of 4.3 and 6.4 for handwashing 5-9 and >10 times per day respectively. The dose-response relation was not observed among subjects using only mild non-industrial surfactants during the day (80).

A follow-up study of apprentice nurses of medium quality, with exposure and symptoms recorded on diary cards reported non-significant associations between HE and use of both soaps and disinfectants (95). While another follow-up intervention study of apprentice nurses of medium quality reported aggravation of skin problems associated to disinfectants with OR 6.1 (71) and another study cross-sectional study of hospital employees of low quality reported disinfectants and detergents/soaps to be the main causes of

OICD (70). Other studies of low quality reported no association between use of disinfectants / local disinfectants (53, 92).

Two studies among hairdressers of medium and low quality respectively reported significant associations between outcomes and the task of shampooing, a typically wet work task, but also a task with exposure to detergents. One of the studies reported an OR of 2.0 of self-reported symptoms for task of shampooing compared to task of cutting (91), while the other study reported association between ICD and hours of shampooing per week without further details (69).

7.3.7 Supplementary evidence

In addition to epidemiological studies experimental studies have demonstrated to be relevant. Application of the anionic detergent Sodium Lauryl Sulfate (SLS) and water has often been chosen in experimental studies as a model irritant detergent in combination with other substances, i.e. so-called tandem irritation studies to study the combined effect of irritant exposures of skin physiology. Assessment of the irritant potential of chemicals has been investigated trough different methods including visual scoring, transepidermal water loss (TEWL), laser-Dobler flowmetry and skin colour reflectance (111). Slotosch et al studied the effects of propanol based disinfectants and detergents on skin irritation and reported significantly more irritation and barrier disruption measured by laser-Dobler flow and TEWL for SLS than for the alcohol based hand rub and protective effect of combined use of SLS and disinfectants (112). This was in line with a study by Loffler et al who performed repeated occlusion tests with ethanol or ethanol and SLS and tandem wash test reporting on erythema, skin hydration and TEWL. They found less skin irritation and a protective effect of alcohol application on previously irritated skin (113). Also, a study by Pedersen et al by daily repeated applications of detergent, alcohol based disinfectants and detergent/disinfectants reported outcome of TEWL and visual score for erythema found an increased irritant response for detergent as compared to disinfectants alone and disinfectants combined with detergent (114).

7.3.8 Conclusion

Results from the presented epidemiological studies on disinfectants and detergents/soap exposure as risk factor of ICD vary, but while not all studies have provided evidence of a negative effect, several studies including experimental studies have indicated irritant effect of detergents/soaps and (disinfectants). In addition, evidence from combined exposure to water i.e. wet work which is most likely also to be the case for multiple studies on wet work exposure where exposure to detergents cannot be separated indicate detergents as an important exposure and cause of ICD.

The overall evidence of a causal association between ICD and exposure to detergent and disinfectants is considered moderate (++), while the overall evidence combined with other wet work is considered strong (+++).

7.4 Exposure to gloves

7.4.1 Design

Exposure to gloves and outcomes related to ICD was reported in 13 papers from 10 epidemiological studies published from 1995-2014, all industry based (53, 66, 70, 77, 78, 80-82, 92-94, 96). Seven of the studies have also been described in the section concerning wet work (53, 78, 80-82, 92-94, 96). Occupations included healthcare work (53, 66, 70, 92-94), cleaning (96), one study on hairdresser apprentices (78, 81, 82), one study in a rubber manufacturing plant and one study in a semiconductor production company (77). One study was a follow-up study (78, 81, 82), the remaining cross-sectional studies.

The size of the studies varied from 140 to 2,352 exposed workers. Two studies included a non-exposed control group (77, 81) , six studies relied on exposure contrast within the exposed groups, while in two studies the exposure contrast regarding glove exposure was ill defined (66, 70).

7.4.2 Exposure source and measure

The study by Lan et al based exposure assessment to gloves on observations, as described for wet work exposure (93). In addition, in one study of cleanroom workers all exposed workers had known exposure to occlusive gloves for most of the work shift (77). The remaining studies relied on self-reported exposure.

7.4.3 Outcome

Five studies included clinical diagnosis (66, 70, 77, 78, 80-82) of which two also included patch tests (66, 70). In three studies diagnosis was self-reported HE in the last 12 months (53, 92, 94), two studies relied on self-reported symptoms (96) or HE was based on self-reported symptoms (93).

7.4.4 Confounding

All but two studies, only reporting on sex and age (53, 96), provided information on atopy, sex and age. Five of the more recent studies performed adjusted analyses and included these along with other occupational risk factors in assessment of use gloves as a risk factor or protective factor for adverse skin outcome (77, 78, 80-82, 93, 94). One study included smoking in adjusted analyses (77). Four cross-sectional studies, all reporting outcome of ICD or self-reported HE associated to use of gloves, did not perform adjusted analyses, though all in univariate analyses reported adverse effects of atopy , age and sex (66, 70, 92).

7.4.5 Quality of the studies

Possible selection bias in the cross-sectional studies reporting on adverse effects of glove wearing is a major risk factor, as a reverse causation cannot be ruled out and may be likely. A higher proportion with prevalent HE or skin irritation may use gloves due to pre-existing skin disease (53, 70, 80, 92-94, 96).

Apart from two studies with observation/measurement of exposure and expert assessment based on known exposure at the work plant (77, 93), all the remaining studies were at risk of misclassification of exposure probably non-differential causing any effects being negative or positive of gloves on skin-irritation to be attenuated.

Bias due to misclassification of outcome due to low specificity or/and low sensitivity of diagnosis may also be present especially in the questionnaire based studies (92-94, 96). Use of gloves, especially rubber gloves, is also a risk factor for ACD and use of natural rubber gloves a risk factor for CU. Risk cannot be assessed at full unless clinical examinations including patch test, and for CU prick test, or serologic test are performed. This misclassification is most likely non-differential, i.e. the risk of misclassification is equal in the exposed and reference population, and the effect of this bias will be a dilution of relative risk estimates toward the null effect thereby attenuating any real association negative or positive to exposure.

Taken together all the studies had some flaws, and none are regarded as highest quality. Three studies are regarded of medium-high quality (77, 81, 93), two of medium quality (80, 94) and the remaining of low quality (53, 66, 70, 92, 96).

7.4.6 Results

Stingeni et al in two cross-sectional studies on employees from the same hospital with clinical examinations including patch tests in the first study reported a high frequency of OCD in 21%, irritant in 95% of cases attributable by self-report or by the authors mainly to disinfectants and gloves, with 12% of workers using gloves reporting "undesirable effects". In the second study only including workers, who used latex gloves, CD attributable to latex gloves was diagnosed in 14%, irritant in 96% diagnosed by a positive "use test" with the suspected glove on a wet hand with appearance of slight erythema and itching and negative patch and prick tests. To explore the etiological role of different glove components in the latex gloves among individuals with use test indicative of ICD, tolerance test using two different substitute latex gloves one with and one without cornstarch powder and an inner lining to protect against latex was performed on a subpopulation and 36% was reported associated to cornstarch powder, 28% to cornstarch and/or latex-protein. In both the studies OCD was reported more frequently in internal and surgical departments and OICD more frequent among nurses and cleaners, in females and younger participants, but no adjusted analyses with contrast to risk factors were performed (66, 70).

Another three cross-sectional studies on cleaners (96) and healthcare workers (92, 94) reported positive associations between use of gloves and significantly increased risk of self-reported symptoms or HE, with

increased OR for self-reported HE with use of protective gloves of 1.87 in one study (92) and of 1.99 for wearing of gloves more than 5 min per use but with no association to frequency of glove use in anotherstudy (94). One study reported a dose-response relation between self-reported symptoms and frequency of glove use reported as seldom, sometimes and often (96).

By contrast no increased risk for ICD was reported in five studies. Uter et al in a follow-up-study on hairdressing apprentices in adjusted analyses for combination with exposure to wet work, reported a protective effect of use of gloves for more than 2 hours per day for wet work exposure i.e. lower risk estimates expressed as OR, when wet work was performed with gloves compared to unprotected wet work (78, 81, 82).

Weistenhöfer et al in a cross-sectional study of 177 cleanroom workers using occlusive nitrile gloves for most of their work shift who were not exposed to additional substances, while reporting increased self-reported work-related skin problems reported no difference in clinical hand eczema score (HEROS) and only transient differences in TEWL compared to non-exposed controls. A positive association for HEROS was reported in univariate analyses to duration of exposure, but disappeared in adjusted analyses including age, sex, previous AD and use of barrier creams (77).

Vermeulen et al in a cross-sectional study of rubber manufacturing workers, in adjusted analyses of association to clinical diagnosed HE and minor dermatitis judged to be mainly irritant reported no effect of glove use (80). Neither did Lan et al or Ibler et al in cross-sectional studies of self-reported HE among heath care workers, which in the study by Lan et al was based on observations of glove use (53, 93). Both the studies by Vermeulen et al and Lan et al reported non-significant OR's ranging from 0.5 to 0.6.

7.4.7 Supplementary evidence

In addition to the included epidemiological studies, supplementary evidence on association between use of occlusive gloves and effect on skin barrier and subsequently possible effect on ICD has been studied in several experimental studies reported in a recent review by Tiedemann et al in 2015(115). The review included eight studies with focus on occlusion alone, seven with focus on occlusion in combination with irritant exposure (some overlapping) and two field studies, one of which has been included in this review (77), and concluded that the negative effect of occlusion in itself is limited, that only extensive and long-term occlusion will cause barrier impairment, while studies investigating combined effect of occlusion and exposure to soaps/detergents indicate that occlusion significantly enhances the skin barrier damage caused by detergents/soaps in a dose-response fashion. Furthermore, a recent unpublished large survey among hospital workers in southern Sweden reported a dose-dependent association between the use of disposable gloves and HE in healthcare workers without a history of atopic dermatitis (personal communication Marléne Isaksson) (116).

7.4.8 Conclusion

Results from the presented epidemiological studies on glove exposure as risk factor for ICD vary with no negative effect of glove exposure in the studies of highest quality. Supplementary information from experimental studies suggests a limited negative effect of glove occlusion by itself, but a probable negative effect of glove occlusion combined with other skin irritants. However, the above mentioned unpublished study may contribute further to evidence of occlusive effect of glove exposure on ICD.

The overall evidence of a causal association between ICD and occlusive glove exposure without other irritant exposures is considered limited (+).

7.5 Metals, metalworking fluids and grease

7.5.1 Design

Exposure to metalworking fluids, related substances and outcomes related to ICD was reported in seven epidemiological studies (64, 65, 72, 74-76, 89) published from 1985-2010, six industry based and one nested case control study within a population study. Work areas included four metalworking factories (64, 65, 75, 76), including two ball bearing factories (64, 75), one hard-metal factory (72) and one study of the car manufacturing industry (74).

Three studies involving clinical assessment and patch tests were all industry-based cross-sectional studies (64, 65, 72). Regarding three studies with clinical assessment without patch tests, two were follow-up performed on metalworking trainees (75, 76) , one additionally with a nested case control study (76) while another study was a nested case control study within a follow-up study (74). One study with outcome relying on self-reported skin symptoms was embedded in a multicentre population follow-up study collecting information on exposure and outcome at follow-up, with baseline information on previous eczema and allergy (89).

Size of the studies varied from 24-776exposed workers, four large studies included >200 (65, 72, 76, 89), two included 79-177 (64, 74), while one small study only included 24 participants (64). Two studies used an external control group (64, 75); the remaining relied on exposure contrast within the exposed groups.

7.5.2 Exposure, source and measure

No studies reported on quantitative measurements of exposure.

In one small study of a ball bearing factory the reported exposure was kerosene, a petroleum product used for cleaning, and exposure contrast within the exposed group was obtained independently of study participants by semi-quantitative expert assessment (64). In one nested case control study, semi-quantitative exposure assessment was based on expert evaluation of individual job risk factors combined with work diaries from individuals (76). Another large study involving workers in hard metal production with reported exposure to cutting oils and fluids when grinding along with various exposures with risk of mechanical irritation (metal pieces and powders) for present exposure, relied on observations on work tasks from day of examinations, while source of previous work tasks is unclear, but probably based on self-reports (72).

Four studies reported on exposure to oil-based metalworking fluids (O-MWF) (65, 74, 75, 89), and (75, 76) water-based metalworking fluids (W-MWF) (65, 76, 89) and mechanical exposures representing mechanical friction (76, 89) and a variation of additional exposures, i.e. metal dust, degreasing agents/solvent cleaners, use of abrasive creams and wet work (74, 76, 89). One reported semi-quantitative expert based exposure assessment (76), two relied on self-reported exposure intensity (74,

89), while in one study it was not clear whether information on exposure intensity was collected from workers or based on expert assessment (65).

7.5.3 Outcome:

Diagnosis of outcome was clinically assessed in all but one study which relied on self-reported outcome (89) and including patch test in three older studies (64, 65, 72). All seven studies provided some information on criteria for diagnosis or grading of diagnosis. Three studies included varying degrees of minor changes/irritant reactions, including typically slight erythema, dryness, and chapping, but without papules, vesicles or fissures (64, 65, 72). One used the definition "clinical dermatoses" combining minor changes and eczema (64), three reported on clinically ICD (74-76), two on mainly mild ICD (75, 76) . In one study outcome relied solely on self-reported symptoms of a rash (89). Outcomes were reported as incidence/incident cases in three studies (74-76), point prevalence (current outcome) in four (64, 65, 72, 75) and prevalence during last year in two studies (89) .

7.5.4 Confounding

The three most recent studies performed adjusted analyses, two including skin atopy, age and gender (74, 76, 89), while one only included age and gender (89). Of the remaining studies one provided no information on atopy, but similar distribution on age and gender among exposed and reference workers (64), one study in univariate analyses reported increased risk of HE among atopic and males and provided no information on age (72), and one a non-significant association between atopy and ICD and no information on age or gender (65). Finally, one small study reported only two with atopy among exposed and similar age and sex distribution among exposed and controls (75).

7.5.5 Quality of the studies

All the studies could potentially be affected by bias or confounding. Three were cross-sectional studies, and while a reverse causality in the case of exposure to metalworking fluids seems unlikely, risk of information as well as selection bias exists, which limits the validity of an exposure causation relation.

This was also the case for the multicentre follow-up study where information on prevalence of self-reported skin rash was collected simultaneously with information on work exposures. As discussed previously selection bias due to healthy worker selection and out of the exposed cohorts and, for both cross-sectional studies and follow-up studies, pre-work self-selection may contribute to bias of the outcome with probable direction toward unity.

Also, the studies may have been affected by misclassification of irritant outcome, most likely in (89) and (74-76)**,** and misclassification of exposure, most likely in the studies where source of exposure was self-reported (74, 89). In addition, small study size in relation to outcome may have contributed to limited statistical power.

Taken together none of the studies were state of the art with good description of studies, highest possible grading of lack of selection bias, misclassifications and accounting for confounders. One study was regarded as medium to high quality (76), three studies were regarded as medium quality (64, 65, 74), two as low quality (72, 75).

7.5.6 Results

A metaanalysis was not performed due to the small amount of studies with different measures of outcome.

Exposure to kerosene was only reported in one study of medium quality, which presented a very high prevalence of clinical dermatoses including slight changes, eczema and defatting dermatitis involving up to 84% of the workers with a clearly increased PR compared to reference workers, while no differences suggesting a dose-response relation could be found when comparing high exposed with low exposed (64).

One large 2.5-year prospective study of Swiss metalworker trainees in a nested case control design in adjusted analyses reported associations between lack of rest days, mechanical work and exposure to cleaning agents containing solvents, while there was no separate effect of exposure to metalworking fluids (MWF) or metal dust (76).

Another nested case control study in the car-industry only including 57 cases in adjusted analyses could not demonstrate any significant effect of exposure to metal-related work exposures (74).

The remaining three studies, two of medium quality and one of low quality reported increased risk of generally mild HE or irritant reactions related especially to W-MWF with prevalence ratios ranging from 1.2 to 3.7 (65, 72), and in one study of incident cases relative differences to non-exposed up to 0.75 (75).

No studies reported on dose response relation between exposure to MWF and irritant skin changes.

7.5.7 Conclusion

The available evidence from epidemiological studies supports a moderate association between MWF and mainly minor ICD. The level of evidence is considered moderate (++).

7.6 Mechanical exposures

7.6.1 Design

Mechanical exposure related to irritant skin reactions was reported in four industry based epidemiological studies published from 1985 to 2000, one nested case control study within a follow-up study (76) and three cross-sectional studies (63, 72, 87). Two of the studies were from the metalworking industry and have also been described in the section on MWF (72, 76) and two were from the construction industry involving exposure to airborne man made mineral fibres (MMMF) (63, 87). The size of the study populations varied from 201 to 2,654 exposed workers.

7.6.2 Exposure, source and measure:

In one cross-sectional study exposure to ceramic MMMF was measured by individual measurements, and measurements of diameters of the ceramic fibres along with examination for content of chromium, cobalt and nickel (63). The other study on construction workers relied on self-reported exposure (87). In one nested case control study expert based semi-quantitative exposure assessments was included (76) and in one large study present exposure was collected by observation, while one cross-sectional study relied solely on self-reported exposure.

7.6.3 Outcome

Diagnosis of ICD and irritant reactions was based on clinical examinations in 3 studies, including patch test in 2 studies (63, 72), while outcome was self-reported eczema and symptoms in one study (87). All studies provided some information on criteria for diagnosis of ICD/HE and/or irritant symptoms.

7.6.4 Confounding

Only one of the studies performed on metal workers included atopy in adjusted analyses of risk for HE (76), while one included age, smoking and exposure to organic solvents in adjusted analyses (87) and two reported increased risk in females or males and atopic individuals without adjusting for these variables (63, 72).

7.6.5 Quality of the studies

All four studies were in some degree prone to bias or confounding. Reverse causality is probably not likely with exposure to mechanical irritants, but the three cross-sectional studies are prone to selection bias due to healthy worker selection which would attenuate results. Misclassification of exposure of both exposure and outcome was most likely in the one study solely relying on self-reported exposure and self-reported eczema and skin irritation (87), and in the study by Fischer et al which did not distinguish me-

chanical exposure of metal and powders from cutting fluids (72). Overall two of the studies was evaluated to be of medium to high quality (63, 76), one of medium quality (87) and one of low quality (72) .

7.6.6 Results

In both the studies on MMMF, an association between exposure to MMMF and ICD was reported. The questionnaire based study by Petersen et al in adjusted analysis including age, smoking and exposure to organic solvents reported a dose response relation between exposure to MMMF and self-reported eczema and itching of the skin (87). increased prevalence's of both acute and chronic ICD was reported among workers exposed to MMMF with an overall PR* for ICD of 6.9 (2.3-20.8) compared to non-exposed and patch test with the ceramic fibres confirming irritancy of the fibres (63).

In the studies of metalworkers, one nested case-control study of medium-high quality adjusted analyses revealed a non-significant trend for a dose response association between hours of daily mechanical work and incident cases of mild HE (76), while one cross-sectional study described an increased prevalence of irritant reactions, PR* 3.7 (2.7-4.9) among grinding workers with mechanical exposure to sharp metal, powders along with cutting fluids and oils compared to other workers (72).

7.6.7 Supplementary evidence

In addition to the included epidemiological studies, experimental studies may be relevant. Tsunoda et al in study of volunteers conducted 24 hour provocations with different continuous glass filaments revealed only transient reactions of the skin at 1 hour after removal of the provocation, but no changes could be observed visually after 24 hours (117).

7.6.8 Conclusion

The reported epidemiological documentation for ICD and skin irritation due to mechanical irritation among workers is scarce and even though the epidemiologic studies consistently reported increased risk of ICD and symptoms at exposure to MMMF or other mechanical exposures, does not allow for a firm conclusion on increased risk and the evidence of a causal association is therefore limited (+).

7.7 Prognosis of ICD

7.7.1 Design

Epidemiological studies on prognosis of OCD including OICD with focus on extent of healing were reported in eleven prospective studies (96, 98, 100-108) and one retrospective cohort study (99) published between 1984 and 2012. Eleven of the studies were based on follow-up of patients from various industries referred to and diagnosed clinically at baseline by dermatologist at specialized dermatology clinics (98, 105, 107), or at occupational dermatology clinics (99, 100, 104, 106), by dermatologists and occupational physicians reporting OCD to a surveillance scheme(101), nationally notified recognized cases examined by dermatologist (108), or notified clinical cases verified by the national institute of occupational health (102, 103). Eight studies concerned patients from various industries. Four studies focused reported on workers from specific industries, one on workers from the food industry (107), one on workers from the metal processing industry (105), one on hairdressers(99) and one industry-based follow-up study of cleaners reported on prognosis of self-reported skin symptoms (96).

The follow-up time of the studies ranged from 0.3-16 years, but most had a fairly short follow-up period and while nine studies included patients with more than one year of follow-up (96, 98-100, 103, 105-107), five of these had a wide range of follow-up i.e. 1-16 years (98), 0.3-10 years (107), 1-5 years (100, 105), and 0.3-2 years (99).

Most studies reported on prognosis of clinically diagnosed OCD including ICD, but only two studies reported exclusively on clinically verified ICD (98, 106). The study size ranged from 51 to 1048 participants, including 16 (105) to approximately 428 (108) with clinically diagnosed ICD. One large study of 1011 cleaners reported on prognosis of baseline self-reported symptoms, presumably mainly irritant due to wet work exposure (96).

7.7.2 Exposures and occupational variables influencing prognosis

The main outcome of interest was prognosis of OICD in relation to effect of change in exposure i.e. by job-change or work tasks after diagnosis, type of exposure/occupation and duration of ICD/OCD prior to diagnosis. Self-reported change of exposure (105), job-change (96, 98-100, 102, 103, 106-108) and/or change of work tasks (100, 107) were reported in ten studies (96, 98-100, 102, 103, 106-108). One study while reporting on the proportion of workers who changed occupation focussed on the influence of current exposure levels based on self-reported exposures on prognosis of ICD (106). Types of exposures/occupation in relation to prognosis was reported in eight studies (96, 99, 102-105, 107, 108), duration of OCD prior to diagnosis in two studies (103, 108), duration of exposure prior to diagnosis (substitute of duration of OCD) in two studies (101, 104).

7.7.3 Prognostic outcomes

The majority of the studies used either healing (clearance) respective persistence (96, 98-100, 102-105) and/or various degrees of improvement respective non-improvement of symptoms (100, 101, 107, 108) as measurement of prognosis of OCD. One study reported prognostic outcome in severity scores including disability of daily living, frequency of relapses, visits to dermatologist and medical treatment (106)

Prognostic outcome was self-reported in most studies (96, 98, 100, 102, 103, 105-108), based on clinical examination only in two studies(99, 101), and in one study clinical assessment of healing was performed in a subgroup of 41% of patients, while the remaining were self-reported in interviews (104).

7.7.4 Confounding

All but three studies provided information on skin atopy (96, 104, 107), in two by excluding patients with AD (98, 106) and analyses for association of skin atopy to prognosis were performed in five studies (100-103, 108), including stratified or adjusted analyses in all but one study (100).

Influence of sex and age was accounted for in all but three studies (98, 105, 107), though only of sex in (106) and age in (99).

7.7.5 Quality of the studies

All the included studies had risk of bias or confounding. Low participation rate at follow-up (98, 100, 106) or missing information on outcome in participants (99) may pose risk of selection bias. While workers could be more likely to participate when still having symptoms of OCD causing an underestimation of overall improvement, selection is probably less likely to be related to exposure variables as change of occupation and work tasks and therefore less likely to produce changes in risk estimates.

Information on exposure to job-change or change of work-tasks was self-reported in most of the studies and may present a risk misclassification of exposure, probably non-differential. At the same time, prognostic outcome in most of the studies relied on self-reported healing or improvement. This could pose a risk of non-differential misclassification causing an underestimation of beneficial effects of work change if workers who had to change jobs are more likely to report a worse prognosis.

Taken together all the studies had minor or major flaws and no studies were regarded as highest quality. Three studies were regarded as medium-high quality (102, 103, 108), five of medium quality(96, 100, 101, 104, 107), and the rest of low quality (98, 99, 105, 106).

7.7.6 Results

The overall proportion of healing of ICD of the cohort studies varied from 18 to 72% (98-100, 102-105) and the proportion who improved varied from 41 to 84% (100, 101, 106-108).

Four studies, two of medium-high and two of medium quality reported a more favourable prognosis for healing of OCD including ICD for workers who changed occupation (96, 100, 103) and/or work task (100, 102) as proxy of lower exposure during follow-up compared to no changes. Another four studies, one of medium (105) and three of low quality (98, 99, 104) reported no association between healing and work changes i.e. change of occupation (98), avoidance of exposure to cutting oil (104) or dis-continuing work as a hairdresser(99).

Malkonen et al in two large Finish studies both of medium-high quality with follow-up of largely the same study-population with 1,048 and 605 participants 6 month and mean 10.5 years after diagnosis of notified OCD at NIOH reported healing of 23% respective 35% of ICD. This was not significantly different from healing of ACD and in multivariate analyses adjusting for type of CD and relevant confounders the studies reported an association between continuation of OCD and no work changes or no change of occupation of 2.7 (1.9-3.8) and 1.6 (1.03-2.34) respectively (102, 103).

Rosen et al reported an overall prevalence of healing of 34% in an Australian study of 334 patients 1-5 years after diagnoses of OCD at a specialized clinic. There was no difference in healing between ICD and ACD. Healing was reported among 28% of those who stayed in the same industry versus 43% of those who changed occupation corresponding to a RR of continuous OCD of 1.3 (1.1-1.5) comparing no change and change of occupation (calculated from data in article) (100). The study also reported a more favourable prognosis with healing of 43% of workers who stayed in the industry and changed work tasks compared to 24% of those workers who did not change, corresponding to a RR for continuous OCD of 1.3 (1.0-1.7) comparing no change and change of work tasks (100).

Nielsen et al in a large Danish two-year follow-up study of 1,011 female cleaners comparing those who left cleaning with continuous cleaners reported OR for continuation of self-reported symptoms of red and rough skin and cracks of 3.3 (1.7-5) and 2.5 (1.4-5) respectively (96).

Two studies, one of medium-high quality (108) and one of medium quality (100) reported on associations between job change and/or change of work tasks and improvement/non-improvement of OCD including ICD. Cvetkovski et al in a Danish study of workers with OHE notified and recognised by the DNBIJ reported an overall one year improvement rate of 41%, where almost 50% had left their job with a strong association between baseline severity of OCD and job loss. They however found no significant improvement in OCD after change of job (108).

Likewise, the Australian study by Rosen et al reported an overall improvement rate of 70% during 5 years of follow-up with non-significantly increased improvement rates of 76% among those who left compared to 67% among those who stayed in the industry. This study however, as with healing reported a better prognosis for improvement among those who stayed in the industry and changed work tasks where 82% experienced improvement compared to 61% among those who did not change work tasks, corresponding to a RR of 2.2 (1.2-4.1) comparing no change and change of work tasks (100).

Duration of OCD prior to diagnosis in relation to healing was reported in two studies both of medium-high quality (103, 108), while duration of exposure prior to diagnosis and association to subsequent healing was reported by one study of medium quality (104). Malkonen et al in adjusted analyses of continuous OHE, mean 10.5 years after diagnosis reported significant associations between persistence of OHE and duration of OHE of more than one year prior to diagnosis, with OR highest at 4.6 (2.4-8.7) for duration of OHE for >10 years (103). In contrast Cvetkovsk et al in adjusted analyses reported no association between aggravating and persistent OHE and duration of OHE prior to diagnosis and Chia et al in stratified analyses reported no association between healing or persistence of ICD and duration of exposure prior to diagnosis (104, 108).

Duration of exposure prior to diagnosis in relation to improvement of OCD during follow-up was reported in one study of medium quality. Adisesh et al in a UK surveillance scheme study on ACD, ICD and mixed diagnoses with no difference in improvement to type of diagnosis, among non-atopic only reported a significantly higher (p=0.03) mean duration of exposure of 9.1 years among patients with non-improvement compared to 5.3 years among those with improvement of OCD (101).

7.7.7 Supplementary evidence

Meding et al in a 15-year population-based follow-up of self-reported prognosis among 868 individuals with clinically verified HE diagnosed in a baseline study in 1983 reported that while two-thirds reported subsequent periods of HE, nearly half during the previous 12 months, the great majority, 74% of the responders with periods of HE reported improvement. Only 3% reported change to another occupation because of HE, and of those 75% reported improvement in HE (118).

7.7.8 Conclusion

Results must be interpreted with caution as most of the included studies were performed on selected populations of patients who had consulted a dermatologist or an occupational physician or were based on notified cases of occupational disease. They therefore probably represent only the most severe cases, and may not be representative for the prognosis of less severe OCD in individuals not seeking specialist medical attention.

With reservations to the above, the available evidence from epidemiological studies supports a poor prognosis for complete healing of OCD including ICD with a high proportion not having complete healing of CD, level of evidence strong (+++), and supports a better prognosis of healing of OCD when exposure is ceased by change of occupation or work task, level of evidence moderate (++).

Though a greater proportion of individuals will naturally experience improvement rather than complete healing, studies on improvement of OCD including ICD in relation to work changes i.e. change of occupation or work tasks are inconclusive due to sparse and conflicting information from studies, level of evidence limited (+).

The level of evidence for an association between long duration of exposure prior to diagnosis and subsequent continuous ICD or non-improvement was limited due to few studies and conflicting results (+).

8 Discussion

8.1.1 Summary of main results

We identified and reported on results and made quality assessment of 50 epidemiological papers from 45 studies presenting results on occupational risk factors for ICD and prognosis of ICD and included supplementary documentation from experimental studies.

Concerning wet work exposure, the available evidence supported an association between wet work, especially frequent wet work and minor ICD in combination with other irritants. No threshold limit could be described. The level of evidence is considered strong (+++)

Regarding exposure to disinfectants and detergents, often in combination with other wet work, the overall evidence for a causal association between the exposure and ICD were considered moderate (++), while the overall evidence for detergent and disinfectants in combination with other wet work were considered strong (+++).

The overall evidence of a causal association between occlusive glove exposure without other irritant and ICD exposures is considered limited (+).

The evidence of a causal association between metalworking exposures and ICD is considered moderate (++).

The overall evidence of a causal association between mechanical exposures and ICD is considered limited (+)

Regarding prognostic outcome of healing of OICD the epidemiological studies support a poor prognosis for complete healing, level of evidence strong (+++), a better prognosis of healing when exposure is ceased or decreased by change of occupation or work task, level of evidence moderate (++), while for improvement of OICD the relation to change of occupation or of work tasks are inconclusive and evidence is considered limited (+).

8.1.2 Misclassification of exposure

Quantitative unbiased independent exposure information is to be preferred to qualitative information (any versus no exposure) since the risk is expected to be dose dependent and therefore less likely to be affected by reporting bias which include irrelevant exposure leading to risk estimates biased towards no effect due to dilution of exposure.

Most of the reported studies have relied on self-reported exposures either in questionnaire or interviews, which may not represent true exposure. Only three studies provided independent quantitative measure-

ments or observations (63, 86, 93), and in three studies semi-quantitative exposure assessment by expert assessment or based on self-reported exposures in diary cards or (40, 64, 76, 95). Two of these studies reported on handwashing among nurses with significant associations between HE and handwashing more than six times during four-hour shift and more than eight times per day with adjusted OR of 3.0 and 2.2 respectively, which strengthen the association (40, 93).

Some of the studies relied solely on comparing different work groups i.e. departments of hospitals without providing information on exposure contrast. While this information may be useful for generating hypothesis, it cannot be used in assessing the degree of risk of exposures and therefore was not included in the text for evaluation of exposures.

Few studies on validity of self-reported exposure to wet work and other irritants have been reported showing variable accuracy. In a study of nurses, Jungbauer et al comparing questionnaires and observation method for duration and frequency of wet work reported low validity of questionnaire based exposures, defined as contact with water or watery soap solutions or wearing of protective gloves over a prolonged period of time. For wet work, the duration of exposure was approximately overestimated by a factor two, while the frequency of exposure to wet work was underestimated by about the same factor (119). In another study of forty geriatric nurses, comparing observations and self-assessment of exposures to water, gloves, hand disinfectants and moisturizers, Anveden et al reported a tendency to overestimate all exposures, especially duration of water exposure and exposure to protective gloves with exposure time being overestimated by 82% and 60% and underestimated by 0% and 3%, while a stronger correlation was found for the number of water exposures, hand disinfections and use of moisturizers, over/-underestimated by 33/10%, 25/18% and 45/5% (120). Likewise, Anveden et al in a study of 40 nurses, mechanics, kitchen and office workers reported moderate correlations to observed exposure for questions regarding frequency of hand washing, but a stronger correlation for exposure times to water, food and occlusive gloves (121).

Relatively, few other studies have measured exposures to wet work and MWF quantitatively. For machine operators exposed to cutting fluids Wassenius et al (122) using a technique based on video recordings of 12 operators with different work methods in different workshops and found a relative wet time that varied between 0% and 100% of total worktime with a significant association between short cycle time and high relative wet time.

Jungbauer et al assessed duration and frequency of wet work exposure using continuous standardized observations of exposure of 41 office cleaners reporting wet work (hand washing and glove occlusion) in 50% of the work period (90 minutes) and a mean frequency of 68 episodes of wet work during a typical 3-hour shift. Glove occlusion constituted two thirds of both duration and frequency of wet work. The study also reported a high variability between individuals for exposure to wet work exposures at similar work tasks (123).

In another study, Jungbauer et al (124), using the same observation methods for the duration and frequency of different wet work activities in 45 nurses, reported substantial differences in wet work expo-

sure depending on the ward, where duration of wet work accounted for 24% of all morning shift, with mean 49 incidents at intensive care units, while duration and frequency in dialysis wards and regular wards respectively were 24%, 49 incidents and 16%, 39 incidents. The study reported short durations of wet work cycles with mean duration of glove occlusion of 3.1 min at regular wards and 6.7 min at intensive care units, classifying nursing as wet work based on frequency of exposure rather than duration. In addition, marked differences in the type of wet work exposure was reported between the different wards, e.g. a higher proportion of gloved activities and lower proportion of patient washing at the intensive care units. (124). Recently, duration of wet work among hairdressers has been assessed by observation in a study by Kralj et al, which in a study of 106 eight hour shifts reported a mean duration of wet work of approx. 2.h, 17 min, with 37% shorter than two hours and 5% longer than four hours, and 18% caused by wearing of occlusive gloves (125). This is in contrast with a recent Danish study among hairdressers relying on self-reported exposure, where 87% had wet hands for more than two hours and 54% for more than 4 hours (126).

In addition, exposure estimates including different exposure, i.e. wet work reported including both frequency of handwashing, duration of wet work with and without exposure to detergents and glove wearing makes it difficult to distinguish between the effect of different exposures.

8.1.3 Misclassification of outcome.

Regarding case definitions for ICD, definitions with low specificity are expected to dilute any real associations with exposure towards the null. Self-reported questionnaire based HE or symptoms of HE have been validated in several studies, revealing a tendency to overestimate the prevalence of HE when using a symptom-based definition with studies of high sensitivity and low specificity, whereas self-reported HE tends to underestimate frequency of HE in general with lower sensitivity and higher specificity (127-130).

Bregnhøj et al in a study validating self-reported HE in the Nordic Occupational Skin Questionnaire (NOSQ-2002) (110) among Danish hairdressing apprentices against clinical examination reported good agreement with a sensitivity of 70.3%, specificity of 99.8% and positive/negative predictive values of 96.3/98.5% ref (131). This standardized questionnaire has also been used in several of studies reported in this review, Ibler et al (53), Flyvholm et al (92) and Mortz et al (47).

Additionally, as described previously, no gold standard of ICD or irritant HE exists, and typically case definitions of ICD historically have been made clinically as an exclusion diagnosis based on no finding of ACD and a temporal assumed relationship to an anamnesis of a supposed relevant irritant exposure (12, 19).

As discussed by Schwenssen et al and Friis et al historically the diagnosis of ICD was applied to a CD with a considerable duration, when careful patch testing had failed to reveal a contact allergy. In recent years however diagnostic criteria for diagnosis of ICD have changed to be defined by significant exposures to known irritant and the temporal relationship between exposure and the dermatitis, i.e. the German wet

work criteria as described in the background section, and including a diagnosis of combined ICD and ACD (19, 132).

They also discussed it is a fundamental problem that the diagnostic criteria for ICD is based on known risk factors i.e. wet work criteria instead of a valid test, with mixing of exposure and a risk of overestimation of the frequency of ICD in occupational settings with high exposures to irritants, demonstrated in a recent study where self-reported exposure to irritants were reported in close to 40% of all in occupation (19, 44, 132).

Another drawback of exposure being included in the diagnostic criteria is difficulties in determination of exposure response relations and different definitions of ICD during the years and studies resembling different outcomes, i.e. some studies reporting on major dermatitis resembling eczema and minor changes/irritant reactions makes it difficult to compare to studies.

Besides, ICD is suspected to play a role in the development of ACD. As dysfunction of the skin barrier is a main feature of any CD it has been found reasonable to assume that this disruption may result in secondary increased sensitization rates to concomitant exposure to allergens with secondary, thereby facilitating ACD (94).

8.1.4 Atopy and other pre-existing non-occupational factors

As described in the background section atopic disposition is a well-known vulnerability factor for increased susceptibility for ICD, with increased odds ratios of a factor three for development of HE. Consequently, accounting for atopy, preferably in adjusted analyses, was included in our quality assessment of the studies. While not all the studies provided information on atopy, the results for exposure response outcome was however not suspiciously different in the studies with information. In fact, some studies when adjusting for atopy showed stronger associations between exposure to irritants and ICD (40, 85). Also, some studies have indicated a healthy worker effect with less susceptible workers entering the work areas with risk of irritant exposures (44, 133).

Gender and age was included in most of the studies, but while some studies reported association to female gender and young age, inclusion of those parameters in the analyses of the studies in general did not provide substantial evidence of change in the effect of occupational irritant exposures.

Private exposures, i.e. housework and minding of young children could be relevant additional exposures which along with occupational exposure could contribute to the overall exposure burden of irritant exposures. Only a few studies included domestic exposures and contribution to the overall exposure burden. While some reported minding of young children or housework to be significant risk factors for ICD (47, 53, 84), others fund no association (71, 93, 94) and the available evidence does not allow for estimating the effect of such exposures. For details on original studies with focus on individual risk factors from 2010 and forward, see table 11, appendix.

8.1.5 Conclusion

This review provides strong evidence for associations between irritant exposures and the development of OICD in relation to wet work exposure, exposure to detergent and disinfectants, moderate evidence for metalwork exposures and limited for exposure to mechanical exposures and gloves. The review provides strong evidence for a poor prognosis of healing, moderate evidence for a better prognosis of healing with cessation or decrease of exposure, limited evidence for improvement regardless of change in exposure and limited evidence for an association between duration of exposure or disease prior to diagnosis and prognostic outcomes.

However, there were few high-quality studies and limitations affected all the studies in varying degrees making comparison and summation of evidence difficult. These limitations included low diagnostic specificity, non-quantitative exposure information, lack of exposure response data and to some extent limited confounder adjustment.

There is a need of follow-up studies focusing on ICD with concomitant quantitative exposure assessment and assessment of ICD using well-defined clinical measures.

9 Tables - results

9.1.1 Table 6 Occupational exposure, outcome based on clinical examinations and patch tests

Table 6	Occupational exposure outcome based on clinical examinations and patch tests						
Author Year Country (ref.)	**Study Design**	**Study population Exposed/ controls (participation rate); Mean age and range**	**Exposure and Exposure Assessment**	**Exposure levels/duration**	**Outcome Diagnostic criteria**	**Covariates accounted for**	**Results PR/RR/OR**
WET WORK OCCUPATIONS							
HEALTH/CARE WORKERS							
Held 2001 (71) Denmark	Prospective study of student auxiliary nurses from 2 schools, f-up after first 10 weeks of practical training. Cohort non-randomly divided in intervention and control group. Questionnaires, clinical exam., patch tests.	Intervention (IG) /controls: Baseline: 61 (81) / 46 (71) ♀ 93%/85%; 28.1 (19-55) / 28.2 (19-45) years F-up:54 (88 %) / 40 (87%)	Self-rep. daily exp. workplace wet work, glove use, moisturizers, and disinfectant agents. Educational program IG group incl. advice on not to use disinfectant agents unless specially recommended, as well as advise on glove use, hand washing and use of moisturizers. Type of disinfectant agents not specified.	IG vs. controls: S. less use of disinfectants. (%/day: no use 21/2, rare use 14/3, 1-3 22/20, >3 43/75. No contrast other work exp. IG vs. controls.	HE/skin irritation Scoring system for extend of HE/skin irritation (erythema, dryness, scaling, vesicles, papules, fissuring& lichenification, max. 74 points) graded mild (1-5 points), moderate/severe (>5 points). Measurements of TEWL during f-up.	AD, sex, age, previous HE, domestic exp. (children<4 year, dish washer), nickel allergy, baseline TEWL values. Adj. analyses no ass. aggravation	CIP HE/skin irritation: IG vs. controls 39% vs. 48% (NS) TEWL increased S in controls, but not in IG. Adj. analysis ass. AD and baseline skin problems: OR **4.89** (1.16-20.64) Adj. analysis aggravation skin problems ass. use of hand disinfectants, OR **6.13 (1.11-38.9**). No ass. to other reported work exp. (incl. in analyses, but does not present numbers or OR) No DRR reported
Stingeni 1995 (70) Italy	CS study of hospitals employees using screening questionnaires, clinical exam. incl. patch and prick skin tests on subjects reporting skin symptoms and/or atopy.	1301(84.9%) ♀ 50.6% Age 39.8; 20-63	Self-rep. various exp. incl. disinfectants, gloves & cleaning products. Department /job category proxy of exp. contrasts in results.		HE, subgroups ICD and ACD HE: objective signs, history and results of skin test. ACD: relevant pos. patch test. ICD: history of correlation of exp. to irritants and onset of cutaneous lesions and no relapse after elimination of	Atopy, sex, age: PR* OCD S for: ♀ vs. ♂**: 2.31**; <31 vs ≥31 years.:**2.23**; atopic vs. non-atopic **1.41** No adj. analyses.	PP HE 28.1%; OCD 21.2%, ICD 20.1%, ACD 1.1%. PR* OCD: Department internal medicine vs: radiological **8.37*** (2.74-25.6); vs. laboratorial **2.22*** (1.46-3.36); vs. surgical **1.57*** (1.26-1.96); PR* OICD: cleaners vs. doctors **2.97*** (1.97-4.46); cleaners vs. nurses **1.20** (0.92-1.55); nurses vs. doctors 2.39 (1.66-3.45) Disinfectants (mainly chlorhexidine gluconate 4%), gloves

Table 6	Occupational exposure outcome based on clinical examinations and patch tests						
Author Year Country (ref.)	**Study Design**	**Study population Exposed/ controls (participation rate); Mean age and range**	**Exposure and Exposure Assessment**	**Exposure levels/duration**	**Outcome Diagnostic criteria**	**Covariates accounted for**	**Results PR/RR/OR**
					implicated substances.		(mainly latex) and among cleaners cleaning products (bleach, detergents and soaps) identified as main causes of OICD. No DRR reported
HAIRDRESSERS							
Guo 1994 (69) Taiwan	CS study 9 randomly selected hairdressing shops with ≥ 10 workers. Interviews and clinical exam. by dermatologist incl. patch test.	98 (91%) 36 stylists, 62 apprentices 19 years (median)	Self- reported /interview: work duration; h/week total & for work tasks incl. shampooing, waving, drying, cutting, blow-drying, cosmetic work and time wearing gloves at work tasks.	Duration work median 24 months. Apprentices/stylists: 91 / 91 % worked full-time mean 73.7 / 73.4 h/week. Work task mean hrs. /week (S diff): Shampooing 15.07 / 0.01; Waving 12.56 / 6.86; Blow drying 7.61 / 21.93; Dying 0.43 / 0.14; Cutting 8.85 / 0; Cosmetic 0.15 /0.	HE, exam. supplemented photographs. HE classified dry "irritant" =MP type and eczematous dermatitis especially involving the fingers. Severity grading, HE: Mild (thickening, scaling), moderate (erythema, itching, hyperpigmentation), severe (oedema, vesicles, fissures, notable erythema).	Allergy, atopy: Patch test pos. 44%, 28% to nickel. Pos. in all with HE fingers. No diff. stylist vs. apprentices or MP type vs. no HE. Atopy no ass. HE or type of HE. No adj. analysis.	HE: PP, PR* apprentices vs. stylists: All HE 98.3% vs. 56.6%, PR* 1.69 (1.28-2.23); moderate/severe HE: 69.3% vs. 27.8%, PR* 2.50 (1.44-4.34). MP type irritant: PP, PR* apprentices vs. stylist: 69.4% vs. 36.1%, **1.9*** (1.2-3.1) MP type ass. time shampooing (h/week), statistics n.r. No DRR reported
FOOD RELATED INDUSTRY							
Teo 2009 (62) Singapore	CS study of kitchen and service worker at 19 restaurants, 3 catering kitchens and 4 fast food outlets (FFO.) Questionnaire, clinical skin exam., patch/prick test when suspected ACD/CU	335 (73%). Restaurants:254; catering 30, FFO 51. ♂ 172, ♀: 163. Mean age n.r 10- 51 (10 years span)	Self-rep. handwashing frequency, exp. to detergents, chemicals, raw food (prawn, fish, crab, meat, garlic etc.)	Hand wash >20 times daily: 36 % (0% FFO, 40% catering, 43% restaurants.	OICD: rash after start of job at sites in contact with known irritants, which improved away from work and no contact with known allergen. Patch/prick test of subgroup with OCD, suspected ACD or CU: one pos. prick test.	Atopy, age, gender, race, duration of service in company, contact with detergent, prawn, fish, crab, meat or garlic, compliance with glove usage.	12 months PP OICD 10% Adj. PR: Handwashing >20 times/day: **2.8 (1.4-5.7);** Contact with squid: **2.6 (1.2-5.5).** Atopy: **3.9** (1.9-8.0). Other covariates NS. No DRR reported

Table 6	Occupational exposure outcome based on clinical examinations and patch tests						
Author Year Country (ref.)	**Study Design**	**Study population Exposed/ controls (participation rate); Mean age and range**	**Exposure and Exposure Assessment**	**Exposure levels/duration**	**Outcome Diagnostic criteria**	**Covariates accounted for**	**Results PR/RR/OR**
Tacke 1995 (68) Germany	Population based register study based on registered recognized cases of OSD for 3 years coupled to number of registered employees in population group. Clinical examinations incl. patch test of cases.	Population, cases OSD, % ♀, % OICD: Bakers: 3,691, 107, 39%, 70% Confectioners: 3,691, 31, 80%, 87% Cooks: 23,252, 79, 70%, 84% Age population n.r. Age of onset OSD median: Bakers 22, confectioners 20, cooks 24 years.	Occupation (baker, confectioner, cook). Time of exposure (month) prior to diagnosis (self-rep.)	Exposure time month median Bakers 26, confectioner 26, cooks 43.	OICD: OSD definition" severe or relapsing dermatosis necessitating cessation of all occupational activities which could be responsible for causing the disease, its relapse or aggravation".	Sex and atopy reported for OSD, but not separately for OICD.	OICD: main diagnosis of OSD in 70% of bakers, 87% of confectioners and 84% of cooks. OICD: CIP* per 10.000 in 3 yrs.: Baker: 134 (104;164); confectioner: 73 (46;101); cook: 28 (22;35) OICD PR* Baker vs. cook: **4.73** (3.40-6.58); vs. confectioner: **1.84** (1.19-2.85); PR* Confectioner vs. cook: **2.58** (1.58-4.09) No DRR reported
Kavli 1987 (67) Norway	CS study at a fish factory of workers employed om fish-stick and fillet production at one fish stick factory. Questionnaire and clinical exam.	fish-stick workers: 122 (61 % of 172, 91% ♀) filet production workers 102 (80% of 150, 84% ♀) 29.8/30.3 years	Occupation proxy of exp. Fish-stick workers: packing of frozen fish-blocks, flour-dust, cardboard boxes, perhaps gloves Filet workers = "Controls": cutting of fish fillets without use of gloves.		ICD Patch test and prick test for ACD (none) and CU used when CD was diagnosed. Diagnostic criteria CD not given.	% of atopic same in occupational groups. No adj. analyses.	ICD fish stick workers / filet workers 5.3% (n=7)/ 2.4% (n=3), PR* 1.95 (0.52-7.35). No DRR reported
GLOVES							
Stingeni 1996 (66) Italy Study subpopulation of (70)	CS study of hospitals employees who usually used latex gloves. Questionnaires, interviews and clinical exam. incl. skin tests on subjects reporting atopy and/or undesirable glove reactions.	922 (90%) ♂ 446; ♀: 476 38.7; 20-59 years Clinical exam. of 128	Latex gloves. No quantitative assessment. Department / job (nurse, doctor, cleaners, laboratory workers, radiology assistant) used as proxy of exp.	N.r.	ICD: HE, neg. patch and prick test for relevant allergens and history of undesirable effects of rubber, itching and erythema at use test with suspected glove on a wet hand.	No adj. analyses Univariate analysis ass. ICD and Age <31 years, female sex (PR* **2.5** (1.78-3.68), ass. HE and atopy (*PR* **1.80*** (1.29-2.51)	PP HE 13.6%; ICD 13%: ♂ 7.2 %, ♀ 17.9 %. ICD PR*: cleaners vs. nurses **1.78 (1.15-2.74);** cleaners vs. doctors: **2.59 (1.48-4.52).** HE PR* departments: internal vs. lab: **1.82 (1.00-3.30**), internal vs. surgical: **1.83 (1.29-5.59)** No DRR reported

Table 6	Occupational exposure outcome based on clinical examinations and patch tests						
Author Year Country (ref.)	**Study Design**	**Study population Exposed/ controls (participation rate); Mean age and range**	**Exposure and Exposure Assessment**	**Exposure levels/duration**	**Outcome** **Diagnostic criteria**	**Covariates accounted for**	**Results PR/RR/OR**
METALWORKING FLUIDS AND OILS							
de Boer 1989 (65) The Nederlands	CS study metalworkers at 10 factories exp. MWF. Interviews, dermatological exam. Patch test when present/previous eczema.	286 (n.r) metalworkers different exp. levels Sex, age: n.r.	MWF (W-MWF n=181, O-MWF n=36, both n=69). Visits with observations on handling of MWF and extend of individual exp. and interview of workers. Usual individual intensity determined as: Freq.: >once per hr. Infrequent.: <once per hr. Variable: combined freq. & infreq.	Freq. exp. 78% Variable exp: 13%	Clinical Dermatitis: minor (slight erythema, chap-ping), major type 1 (widespread erythema, induration), type 2 (eczema). Irritant skin changes/ICD: Dermatitis /eczema + neg. patch tests.	Allergy (2.8% ACD excluded analysis) Atopy NS irritant changes.	PP 14% CD, 11% ICD, 58% minor or major irritant skin changes. Minor/major irritant skin changes freq./variable vs. infreq. exp. W-MWF: PR* **2.90 (1.22-6.92)**; Freq./variable exp. W-MWF vs. O-MWF: PR* **2.34 (1.29-4.25**). No ass to freq. of O-MWF. No DRR reported
Jee 1986 (64) Taiwan	CS study of female workers of Ball Bearing factory and reference workers at a zipper-manufacturing company. Clinical exam. and patch test of selected subjects.	79 (35 heavy and 45 lightly exp.) / 263 All ♀ 18.9 /20.3, 16-26/15-29 years	Kerosene (petroleum product used for degreasing). Semi-quantitative, expert judgement by departments. heavy/lightly exp.: 35/45	Heavy exp. approx. 5 hrs. a day. Light exp. less hrs. a day (not specified). Heavy exp. wore gloves 3 hrs. daily at most exp. process.	Clinical Dermatoses i) Erythema: erythema +/- desquamation over interdigital spaces ii) Eczema: papules, papulo-vesicles, scaling and thickening. iii) Defatting dermatitis: pallor, dryness and fissuring	Sex, age Allergy: Patch test on 5 workers with severe eczema, 1 pos. to non-related product.	Dermatoses/Eczema exp. vs. controls 84%/15% vs. <1%; PR* 220 (31-1558)/ 39.9 (5.3-302) Dermatoses/eczema high vs. low exp.: PR* 1.17 (0.97-1.41) / 1.56 (0.54-4.47) No DRR reported
Fischer 1985 (72) Sweden	CS study of workers in a hard-metal factory by interview and dermatological exam. Incl. patch tests for substances in the industry and home environment.	776 (97%) ♂**:** 57% Age n.r.	Present and previous work-activities at plant focusing on working as a grinder with various functions primarily wet and oil grinding vs. other work-activities. Grinding described with mechanical exp. to sharp metal, powders, and cutting fluids and oils. Source of exp. assessment for present exp. observed work task on the day of exam. Source of previous work tasks not given seems to be self-rep.		Present or history of HE/Dermatitis and "irritant reactions" HE definition: hands variably show erythema, scaling, crusting, papules, and/or vesicles. "Irritant reactions": when hands show dryness and light cracks, erythema and scaling without papules and vesicles and rapid improvement on vacations and weekends.	Increased risk of HE in males, atopic. More contact sensitivity to relevant allergens among HE (18%) vs. irritant reaction (5.7%) and no symptoms (5.5%). No adjusted analyses.	PP: 9.9% current HE, 12.4% previous HE, 14.2% current "irritation", 3.9% previous irritation. No diff. HE in present work activities. Current or previous skin reactions for present work as grinders vs. other groups of workers, **PR*:** HE: 0.88* (0.64-1.20) Irritant reactions: **3.66* (2.73-4.90)** HE or irritant reactions: **1.76* (1.43-2.06)** Current or previous skin reactions for present or previous wet oil grinding vs. dry grinders and others, **PR*:** HE: **1.93 (1.46-2.56)** Irritant reactions: **3.38 (2.33-4.88)** HE or irritant reactions: **2.65 (2.15-3.26)** No DRR reported

Table 6	Occupational exposure outcome based on clinical examinations and patch tests						
Author Year Country (ref.)	**Study Design**	**Study population Exposed/ controls (participation rate); Mean age and range**	**Exposure and Exposure Assessment**	**Exposure levels/duration**	**Outcome** **Diagnostic criteria**	**Covariates accounted for**	**Results PR/RR/OR**
FIBRES							
Kiec-Swierczynska 2000 (63) Poland	CS study at 6 factories manufacturing or processing L-2 and L-3 ceramic fibres.	226 /43 (n.r) ♂: 122/20; ♀ 104/23 Age 41.2/40.2, 21-61/n.r.	127 individual measurements of total and respirable dust. Measurements of diameters of ceramic fibres and analysis of fibres for determination of content of chromium, cobalt and nickel.	Range total dust 0.2-33.9 mg/m^3 Fibres for patch test: Thermowool fibres: no fibres >3µm L-2 fibres: 6.3% of fibres >3µm. L-3 fibres: 11.1% of fibres >3µm. Ceramic fibres with trace amounts of chromium and cobalt.	ICD diagnosed clinical Acute ICD: transient (2-3 days) maculae or papulae and small crusts on the trunk and extremities. Chronic ICD: diffuse constant erythema, numerous telangiectasias on face neck, trunk and behind the auricles) Patch test of exp. incl. relevant allergens and patch test for irritative response to ceramic fibres.	Sex, ICD more frequent in females. Few positive patch tests for allergens most evaluated as non-occupational.	PP, RD* or PR* exp. vs. controls All exp. reported strong itching of skin. ICD: 48.2%, vs. 7%, PR* **6.91* (2.30-20.8)** Acute ICD: 30.5% vs. 0%, RD* 0.31* (0.25-0.37) Chronic ICD: 26.1% vs. 7%, PR* **3.74* (1.22-11.4)** Patch test confirmed irritative activity of ceramic fibres with erythema persistent for 96 hrs. in 19.5%. Irritant activity of fibres correlated to thickness, with higher irritancy of filaments containing fibres >3µm No DRR reported

Diagnoses: ACD: Allergic contact dermatitis; AD: Atopic dermatitis; CU: Contact urticaria; HE: Hand eczema; ICD: Irritant contact dermatitis; OCD: Occupational contact dermatitis; OICD: Irritant occupational contact dermatitis; MP: anatomic location metacarpophalangeal joint = knuckles; OSD: Occupational skin disease

Exposures and confounders: exp: exposure; MWF: Metal working fluids; W-MWF: water-based MWF=soluble MWF; O-MWF: oil-based MWF=neat/insoluble MWF

Study characteristics: adj: adjusted; ass: association; CIP: Cumulative incidence proportion; CS: cross sectional; diff: differences; DRR: dose-response relation; f-up: follow-up; exam: examination; freq: frequent; hrs.: hours; IG: Intervention Group; incl: included; neg: negative; n.r: not reported; NS: non-significant; OR: odds ratio; PP: Prevalence proportion; PR: Prevalence ratio; S: significant; self-rep: self-reported; TEWL: Transepidermal water loss; vs.: versus ; *Calculated from data provided in article

9.1.2 Table 7 Occupational exposure, outcome based on clinical examinations, no patch tests

Table 7	Occupational exposure outcome based on clinical examinations, but no patch tests						
Author Year Country (ref.)	**Study Design**	**Study population Exposed/ controls (participation rate); Mean age and range**	**Exposure and Exposure Assessment**	**Exposure levels/duration**	**Outcome Diagnostic criteria**	**Covariates accounted for**	**Results PR/RR/OR**
WET WORK OCCUPATIONS							
HEALTHCARE WORKERS							
Callahan 2013 (85) USA	6-month prospective study of volunteer HCW, washing hands ≥8 times/day. Baseline questionnaire and patch test for skin irritants. Clinical exam. at 1 month interval.	113 volunteers, % of pop. n.r. 102 (90%), 12 with baseline ICD of hands incl. analysis. ♂ 64% Age 32 (9.6)	Self-rep baseline daily freq. of handwashing. Season (cold and warm)	Times daily handwashing mean (SD): 12 (5.7)	ICD hands diag. clinical**.** ICD classified active dermatitis/eczema & minor dermatitis (erythema, slight chapping and scaling).	Atopy, age, sex, ethnicity, indoor humidity, use of gloves and sanitizers. Response patch test irritants.	CIP ICD hands 51%. Participants ICD mean 1.2 (1.4) times during study. Adj. PR ICD: **DRR** Handwashing freq: **1.03 (**1.00-1.05) Handwashing ≥10 times/day: **1.55** (1.01-2.39). Season (cold vs. warm)): **1.88** (1.12-3.14) Adj. IRR ICD: **DRR** Handwashing freq:**1.04** (1.01-1.07) Handwashing ≥10 times/day: **1.95 (**1.16-3.29) Season (cold vs. warm): **2.76 (**1.35-5.65)
FOOD RELATED INDUSTRY							
Bauer 2001 (84) Germany	Prospective 3 years cohort study apprentices, f-up of (83) 1996-99.	63 (69%) at all 4 exam. after start of training. ♀: 57% 19.5 (0.99) years.	As (83)	1.2% wet work + hand washing >20 times/day 56% resp. 37% various cleaning procedures >1 hr. per day. 40% dough preparation >1 h./day 18% fruit handling >1 hr./day	As (83)	Sex, Atopy, flexural dermatitis, previous HE, leisure activities. S ass. to HE reported for all, but sex.	PP 3-year OCD hands 27.5%, 21.7% ICD. Period P HE study: 41.3%. Adj. analysis at 3-year, OR Wet work +Hand washing >20 times/day: **1.2 (**1.05-4.77) Handwashing >20 times/day, NS ass. 1.2 (0.22-4.24), Wet work: up to 4 hrs./day NS ass.: 1.2 (0.99-1.99) No ass. handling of fruits, glove us. No DRR reported

Table 7	Occupational exposure outcome based on clinical examinations, but no patch tests						
Author Year Country (ref.)	**Study Design**	**Study population Exposed/ controls (participation rate); Mean age and range**	**Exposure and Exposure Assessment**	**Exposure levels/duration**	**Outcome** **Diagnostic criteria**	**Covariates accounted for**	**Results PR/RR/OR**
Bauer 1998 (83) Germany	Prospective 1 year cohort study bakers-, confectioners and bakery shop assistant apprentice 1996-97. Interview and clinical exam.	91 2-4 weeks after start of training. 79 (87%) ½ year., 63 (69%) 1 year ♀: 57% 17.7 (1.34) years.	Self-rep freq. hrs./day work tasks (<1 h, 1-4 h, >4 h), cleansing habits, glove use and leisure time activities. Work tasks incl. wet work (cleaning and wet dough) and fruit handling. Profession.	Not reported.	HE and ICD at clinical exam. HE defined mild (erythema, scaling), moderate (infiltration and papules), severe (vesicles and fissures). *Atopic skin diathesis assessed by "Erlangen Atopy Score"*	Atopy (non-consistently ass. HE), previous HE, sex. No adj. analysis.	PP OCD hands, ICD 17.5% (n.r) at 2-4 weeks; 29%, 25.3 % at ½ year.; 27%, 19% at 1 year. HE, exp. OR Fruit prep >4 hrs. at f-up ½ year, S, p<0.04, NS >1 hr. at 1 year. Handwashing >20/day: at 1 year: 2.95 (0.85-10) Cleansing >1 hrs.: at 1 year: **1.7 (1.3-2.1)** No DRR reported
HAIRDRESSERS							
Uter (POSH STUDY) 1999 (82) 1999 (81) 1998 (79) 1998 (78) Germany	Prospective cohort study of hairdressing apprentices recruited in 3 waves 1992-1994 at 15 vocational schools followed for 3 years by 3 exam. Office workers collected as a control group	2352 / 111 (91.5%, n.r) at baseline, 8 weeks training. 1 year f-up: 1717/40 (73% /36%) 3 F-up: 1.134/68 (48%/61%) Age: Mean 17,1(16-21) Sex: 94 % women	Self-rep in standardized questionnaire. Calculated individual daily time of unprotected wet work and of glove wearing. High wet load, mainly caused by freq. shampooing and permanent waving without wearing gloves.	wet work/ glove wearing: hours pr. day <2 h/ >2 h <2 h /<2 h >2 h /<2 h >2 h/ <2 h hand washing less than 10 t/day min. 10 t/day	Operational definitions for skin changes used. Classified as Mild Moderate Severe In the analyses of risk factors used as ``skin changes (any degree) and HE.	Atopy score, age, sex, past HE, past flexural eczema, humidity. Atopy score ass. increased risk of skin changes. Selective inclusion in hairdressing cohort of non-atopic, selective dropout of atopic.	Reports almost exclusively irritant skin damage. Incidence per 100 person/year any skin changes and HE 34.3 and 15.2 respectively PP any skin changes/HE %: 35.4/12.9 at baseline, 47.5/23.5 at 1 year. f-up, 55.1/23.9 at 3. year f-up. Unprotected wet work >2 h per day was the major occupational risk factor: PR 3-year f-up wet work/glove work, >2 h/day & glove work < 2 h/day: 1.13 (1.01-1.25) Adj. analyses at 3 years f-up, OR: Hairdresser vs. office worker :**1.7** to **3.1** Wet work /glove wearing h/day <2h/<2h: 1.4 (0.5-4.3), ≥2h/≥2 h: **1.6 (**1.1–2.3), ≥2h/<2 h: **1.8** (1.2–2.6), Handwashing >10/day: 1.1 (0.9-1.4) No DRR reported

Table 7	Occupational exposure outcome based on clinical examinations, but no patch tests						
Author Year Country (ref.)	**Study Design**	**Study population Exposed/ controls (participation rate); Mean age and range**	**Exposure and Exposure Assessment**	**Exposure levels/duration**	**Outcome** **Diagnostic criteria**	**Covariates accounted for**	**Results PR/RR/OR**
GLOVES							
Weistenhöfer 2015 (77) Germany	CS study of workers in semiconductor production company. Interviews, dermatological exam. and measurement of TEWL.	177/146 (91%) Age 42/45 ♂ 58%/55% 20-61/19-59	Cleanroom workers using occlusive nitrile gloves most of work shift, which were not exp.to additional hazardous substances compared to administration workers.	Exp. wore gloves ≥ 2 hrs. during day of investigation Duration of exp.: Month:<12, 13-24, 25-90, <=91	HE. Diagnosed clinical using validated score for HE: HEROS (Hand Eczema score for Occupational Screening, scoring from 0-2260 points)	Age, sex, previous AD, smoking and use of barrier creams in adj. analysis. (♀higher use of barrier creams lover HEROS)	Unadjusted no diff. HEROS exp. vs controls median (range) 14.8 (1-37) vs. 15.5 (2-48). Pos. ass. HEROS and duration of glove wearing, but no diff. between highest exp. and controls. Adj. analyses: No ass. HEROS and use of gloves, days of work since time off or total duration of work in clean room. Transient (30 min) increased TEWL exp. vs. controls. Adj. ♂ sex only risk factor increased TEWL. No DRR reported
WET WORK VARIOUS INDUSTRIES							
Vermeulen 2001(80). The Nederlands	CS study of random workers at 9 rubber manufacturing companies. Clinical exam. dermatologist. Interview.	202 (90%) All ♂ 37.6 (9.1), 19-60 years	Water, detergents/surfactants, gloves and, various chemicals. Self-rep. freq. of hand washing, freq. and type of surfactants in standardized interview by dermatologist. Surfactants verified and categorized as mild (household soap) or industrial surfactants (scrubbing particles ±organic solvent) Personal measurements of dermal exposure to cyclohexane-soluble matter (CSM) with dermal pads. Use of protective gloves evaluated by observation. Reported domestic exposure evaluated by experts for irritancy.	Median CSM 31.7ug/cm2 classified as high exposure.	HE Classified major dermatitis (active HE) when erythema, papules, vesicles and fissure, minor dermatitis when erythema, slight chapping and scaling of the skin IgE for latex allergy.	Sex, age, atopy, domestic skin exp. irritants. Ass. domestic activities and minor dermatitis, OR 4.33 (1.72-10.9) Only 2 ~1% self-reported allergic reaction rubber. No pos. IgE for latex.	PP 6.9% HE (major dermatitis), 28% minor dermatitis, 17% traumatized skin. 64% of major and 43% of minor dermatitis reported work-related. ICD interpreted as predominant due to overall absence of self-rep. reactions to rubber goods and chemicals. Adj. analysis major/minor dermatitis, OR: High dermal exp. CSM: 2.15 (0.58-7.95) / 0.82 (0.40-1.69) Handwashing/day: 5- 10: 0.53 (0.11-2.66) / **3.09** (1.16-8.21) >10: 1.18 (0.30-4.62) / 2.27 (0.92-5.56) Industrial surfactant use: 0.64 (0.19-2.21) / 1.92 (0.91-4.02) Glove use: 0.61 (0.18-2.11) / 0.58 (0.27-1.23) **DRR** between freq. of hand washing and minor dermatitis when use of industrial surfactant (no ass. when use of regular soap/mild surfactant) Freq. of handwashing/day& industrial surfactant, OR: 5- 9: **4.27 (**0.90-20.3); >10: **6.38** (1.35-30.2)

Table 7	Occupational exposure outcome based on clinical examinations, but no patch tests						
Author Year Country (ref.)	**Study Design**	**Study population Exposed/ controls (participation rate); Mean age and range**	**Exposure and Exposure Assessment**	**Exposure levels/duration**	**Outcome** **Diagnostic criteria**	**Covariates accounted for**	**Results PR/RR/OR**
METALWORKING / FLUIDS AND OILS							
Berndt 2000 (76) Switzerland	Prospective 2.5-year cohort study with nested CC study of metalworker trainees at 24 metalworking factories without pre-existing HE. Clinical exam. at 6-month interval.	201 exp. (100 %). 47 incident cases matched 3 controls with same duration of exp. All ♂ Age young	O-MWF, W-MWF, mechanical irritation (friction and pressure), metal dust, cleaners (+/- solvents). Semi-quantitative exp. assessments (hrs./week) based on expert judgement on exp. in individual jobs risk factors skin irritation combined with work diary from individuals. Schooldays weekly with theoretical classes without exp.	Average daily exp. mechanical irritation and metal dust and O-MWF highest first ½ year. High mean exp. W-MWF approx. 4 h/day with slight increase during f-up.	Incident mild HE determined by clinical exam. Case definition: at least one hand with erythema and scaling, vesicles, excoriations, papules or exudation.	Sex, age, domestic exp., smoking. Atopy (history of flexural eczema) ass. HE (OR 9.1/12.0).	CIP 2.5 year: 23%. First ½ year: 9%, thereafter 6, 6, 3 and 3%. HE cases vs. controls: **S (p<0.05**) ass. daily duration of mechanical exp., fewer schooldays (recovery time) and atopy. No ass. other work- or domestic exp. or smoking. Adj. analyses OR for whole period / 0.5 year. prior to diagnosis: School days/week ≤1.5: **2.64** (1.23-5.67) / **2.81** (1.20-6.56); Mechanical work (hrs./day): 1.35 (0.98-1.86) **trend** / -; Cleaners with solvent (hrs./day: - / 1.44 (0.99-2.08) **trend** p≤0.1.
Goh 1994 (75) Singapore	Prospective 6-month cohort study of newly recruited machinist at ball-bearing factory and paramedic controls.	24/27 (n.r.volunteers) ♂ % 96 / 81 20/23; 18-27/17-35 years	O- MWF. Qualitative industry based exp. assessment. Incl. machinist without previous exp. cutting fluids from grinding and turning departments with daily exp. O-MWF.	Daily.	Incidence reported as point prevalence ICD at 3 weeks interval during study. Diagnosed history and clinical findings Classified Mild: <25% hand, Moderate: >25% hand. Argue that results with mainly mild indicate most/all dermatitis ICD.	Atopy, Age, sex. No adj. analyses, but small diff. exp. and controls. Only 2 atopic exp. TEWL, higher exp. No diff. PR ass. to basal TEWL.	PP ICD mainly mild exp. T_{week}: T_0:0%, T_3:38%, T_6:77%, T_9-T_{30}: 50%. PP controls all 0. RD* exp. vs. controls T3: **0.38** (0.18-0.57) T6: **0.75** (0.58-0.92) T9-T30: **0.5** (0.30-0.70). No DRR reported

Table 7	Occupational exposure outcome based on clinical examinations, but no patch tests						
Author Year Country (ref.)	**Study Design**	**Study population Exposed/ controls (participation rate); Mean age and range**	**Exposure and Exposure Assessment**	**Exposure lev-els/duration**	**Outcome Diagnostic criteria**	**Covariates accounted for**	**Results PR/RR/OR**
MECHANICS – CAR INDUSRY							
Apfelbacher 2010 (74) Germany	Nested CC studies on prevalent cases of HE and subgroup of ICD from 13- year f-up studies in the car manufacturing industry (PACO1 and 2) Controls were random samples of non-cases from same population. Question-naire, interview, exam. by dermatologist.	Cases/controls ICD 57/120, ♂ 86.0 % / 84.2%. Age 28.9/29.3 years Population in car industry incl. all workgroups incl. metalworkers and office workers.	Wet work hrs./day: occup. & do-mestic exp. wet work soiling, direct water contact & occlusive gloves. Dry skin soiling hrs./day, any exp. W-MWF, O-MWF, solvents, epox-ide, metal dust. Frequency use cleaning pastes/abrasive pastes and creams. Qualitative self-rep. current exp. in interview by health scientist.	Cases / controls %: ≥ 2 hrs./day wet work: 49.1 / 31.7; dry skin soiling ≥ 3 hrs. 17.5 / 11.7; W-MWF: 15.8 / 10.0; O-MWF: 43.9 / 33.3; Solvents: 21.1 / 15.0; office work: 15.8 / 32.5	ICD: HE recorded as irritant by dermatologist. HE when erythema and (vesicles, scaling, papules, ero-sions/fissures or lichenifica-tion).	Atopy (ASD), flexural eczema last 10 years, age, sex, domestic exp. Atopy ass. ICD OR: 1.84 (1.20-2.80)	Cases vs. controls: Lower PP for office job, higher for wet work >2 hrs. **OR* 0.39** (0.15-0.91) and **2.08** (1.04-4.18). Adj. analysis no S. ass to occupational or domestic exp. OR wet work ≥ 2 hrs.: 1.62 (0.78-3.37). No DRR reported
VARIOUS INDUSTRI /EXPOSURES							
Chou 2004 (73) Taiwan, China	CS study of 110 workers at 8 departments in rayon factory.	81 (CS_2: 13; H_2SO_4: 2; combined: 66) /29 (n.r) Sex, age: n.r	CS_2, $H2SO_4$ Expert judgement based on field study of work processes in depart-ments and information from fore-man. Exp. dichotomized +/- exp.	CS_2: pure min. 6-8 times/shift H_2SO_4: 20% 6-8 times/shift Combined: solution CS2 (2,2 g/l) & 10% H_2SO_4	HE Clinical diagnosed by dermatologist. HE when skin with clear eczematous picture of erythema, papules vesicles and fissures. According to definition by (80).	Handwashing habit & glove use given for 37 workers. No adj.	PR HE especially palms, exp. 50-64%, controls 3.4% HE Exp. vs. controls, PR*/OR: CS_2: **17.9*** (2.5-128) / 44.8 (6.4–934) H_2SO_4: **14.5*** (1.4-155.) / **28.0** (0.8–1429) Combined. **18.5*** (2.7-128) / **49.0** (9.5-901) No DRR reported

Diagnoses: HE: Hand eczema; ICD: Irritant contact dermatitis; OCD: Occupational contact dermatitis
Exposures and confounders: HCW: Healthcare workers; exp: exposure; CS_2: carbon disulphide; H_2SO_4: sulfuric acid; MWF: Metal working fluids; W-MWF: water-based MWF=soluble MWF; O-MWF: oil-based MWF=neat/insoluble MWF
Study characteristics:adj: adjusted; ass: association;, CC: case control; CIP: Cumulative incidence proportion; CS: cross sectional; diff: differences; DRR: dose-response relation ;exam: examination; f-up: follow-up; freq: frequent; hrs.: hours; incl: included; n.r: not reported; NS: non-significant; OR: odds ratio; PP: Prevalence proportion; PR: Prevalence ratio; S: significant; self-rep: self-reported; TEWL: Transepidermal water loss; vs.: versus;
*Calculated from data provided in article

9.1.3 Table 8 Occupational exposure, outcome self-reported

Table 8	Occupational exposures – outcome self-reported						
Author Year Country (ref.)	**Study Design**	**Study population Exposed/ controls (participation rate); Mean age and range**	**Exposure and Exposure Assessment**	**Exposure levels/duration**	**Outcome** **Diagnostic criteria**	**Covariates accounted for**	**Results PR/RR/OR**
WET WORK OCCUPATIONS							
CLEANERS							
Mirabelli 2012 (97) Spain	CS study (EPIASLI2) in 2008 of cleaner and non-cleaners at 37 cleaning companies. Nested CC on subpopulation for clinical validation of questionnaire.	818 (**16%),** 693/125 ♀: 581 (84%)/92 (74%) Age 45/42; 22-61/18-65 Controls incl. 68 never cleaners and 57 former cleaners.	Self-rep: Cleaner/non-cleaner Freq. various work-sites/activities and use of various cleaning products (ammonia, bleach, hydrochloric agents, degreasing agents, dust mop products, glass cleaners, rug cleaners, polishes, perfumed products, multi-use products, etc.)	Numerous reported. Selected exp. last 12 month: Use of hydrochloric acid: 36%, use of dust mob products 30%.	HE last 12 months. Definition HE: ≥1 of 5 possible self-rep skin symptoms. Validation symptom-based HE: clinical exam. nested CC (70): sensitivity 0.82, specificity 0.62, pos. pred. 0.41, neg. pred. 0.92	Age, sex, previous eczema, previous allergy, country of birth, freq. glove use, cleaning own home	HE 28% cleaners vs. 18% controls Adj. PR: Exp. vs. C: **1.60 (1.03-2.47)** Separate adj. analyses on each of 12 cleaning worksites and 12 exposures comparing exp. last 12 month to controls, reported **PR significant** for outdoor areas, schools, residential areas, and construction sites range **1.77-1.87** and S for use of hydrochloric acid **1.92** (1.22-3.03) and use of dust mop products **1.75** (1.11-2.75) as well as for freq. use of several products. Other worksites and exp. PR~1.6 as previous analyses of exp. vs. controls. No analyses without control group comparing low-exposed to high-exposed. No analysis adjusting accounting for influence of individual cleaning agent. No DRR reported.
Nielsen 1996 (96) Denmark	Baseline CS study of female cleaners at 271 public institutions in 1989 regarding risk factors of skin symptoms. (3-year cohort study prognosis reported in table 10)	1166 (51%) at baseline. Age n.r.	Self-rep proportion of wet work and use of protective gloves at workplace and at home. Hrs. of weekly wet work calculated from information on work hours and self-rep. proportion wet work.	Wet work at workplace hrs. per week baseline: <1:19%; 1-10:25%;11-20:33%; 21-30:16%; 31-40: 6%, >40:1%. Use of protective gloves: often:26%; sometimes:16%; seldom:58%	12-month prevalence self-rep skin symptoms incl.: red and rough skin; cracks, itching, vesicles. No clinical validation.	Adj. age, sex (all ♀), wet work at home (NS) No account atopy.	Baseline CS study Adj. **DRR** hrs. per week of wet work and use of protective gloves and different skin symptoms Hrs. wet work and vesicles, OR: 1-10:1.4; 11-20:1.6; 21-30:**2.4;** 31-40:2.0; >40:0.9. Use of protective gloves and vesicles, OR Seldom: 1; sometimes **3.1**, often **4.2**

Table 8	Occupational exposures – outcome self-reported						
Author Year Country (ref.)	**Study Design**	**Study population Exposed/ controls (participation rate); Mean age and range**	**Exposure and Exposure Assessment**	**Exposure levels/duration**	**Outcome Diagnostic criteria**	**Covariates accounted for**	**Results PR/RR/OR**
HEALTHCARE WORKERS							
Visser 2014 (95) The Nederlands	1-3 years prospective cohort study of apprentice nurses from 15 vocational schools. Entry questionnaire and diary cards during f-up recording exposure and skin symptoms.	721 (~50% baseline), 533 (73%), f-up 1,2 or 3 years, 445 without previous HE. Age median (25-75%): 19.5 (18.3-20.9) years ♀ 90 %	Wet work activities: hand washing, use of alcohol rubs, wearing gloves, other contact with water, soap and disinfectants reported/measured freq. and duration by 383 participants on diary cards every 2-4 weeks.	Wet work >2 hrs. or hand washing >20 times per day in 29%. Varied health sector, exceeded by 43% in hospital traineeships, 17 % in nursing homes, 11% nursing homes, 6 % in psychiatry.	HE: self-rep. fissures combined with redness, itch or scaling, vesicles or papules for >3 days recorded on diary cards every 2-4 weeks. Mild HE: combination self-report. redness, scaling, fissures, vesicles or papules of any duration. No clinical validation.	Higher proportion of history of AD, rhinitis and asthma among participants compared to non-participants. No adj. for atopy.	KIP HE f-up 18%, most in first traineeship. IR HE/100 person-year in traineeship 36.7 first vs. 13.7 second/third IR HE/100 person-year: 20.0 first vs. 8.5 second/third PP first, second and third year of study mild HE 33, 29 and 31% HE 21, 25 and 33%. Adj. analysis HE during traineeship wet work activities, OR: Handwashing ≥8 times/day: **1.5** (1.02-2.25) Soap exp. ≥4 times/day: 1.5 (0.97-2.30) Disinfectants ≥2 times/day: 1.1 (0.69-1.79). No ass.to other wet work activities. No DRR
Visser (40) 2014 The Nederlands	As (95), same study population. Incl. genotyping most common FLG loss-mutations.	As (95) 626 DNA samples, 596 genotyped for four FLG loss mutations (R501X, 2282del4, R2447X and S3247X)	As (95) incl. only freq. of hand-washing in analysis. Self-rep. work in a side job (i.e. healthcare, catering) with wet work exposure.		HE: as (95)	Atopy, FLG-mutations, freq. hand washing at home.	Adj. analysis HE & HE during traineeship, no previous HE or wet work exp. OR: Handwashing ≥8 times/day: **2.2** (1.2-4.2) & 1.4 (0.6-3.4) Side job wet work >8 hrs./week: **1.8 (***1.1-2.9)* & 1.9 (0.9-4.2)

Table 8	Occupational exposures – outcome self-reported						
Author Year Country (ref.)	**Study Design**	**Study population Exposed/ controls (participation rate); Mean age and range**	**Exposure and Exposure Assessment**	**Exposure lev-els/duration**	**Outcome** **Diagnostic criteria**	**Covariates accounted for**	**Results PR/RR/OR**
Lee 2013 (94) Korea	CS study in hospital of nursing staff using questionnaire and patch testing on subpopulation of workers reporting HE.	525 (75%) ♀ 97.1 % 38.8; 21-58 years.	Self-rep: daily hand washing freq., daily glove wearing time, daily use of hand moisturizer, use of alcohol based skin rubs, duration of em-ployment, department	Hand washing: 4 groups (<10->30), 35% >20 times a day. Glove wearing time: 3 groups (<1 min->5min a day), Use of moisturizer 5 groups 0->10 times a day.	HE: Self-rep. HE last 12 months, symptom-based HE (pos. reply 1 of 6 symp-toms). No clinical validation. ACD: relevant pos. patch tests in 43 (61.4%) of subgroup of 70 (43%) of workers with HE. Sensitiza-tion mainly to nickel, cobalt, thiomersal, ammoniated mercury and potassium, but also to substances in disinfectants.	Atopy, age, sex, history of rhini-tis/asthma. hours of housework	PR HE 31.0%; PR symptom-based HE: 75.6%. No ass. HE: department, Adj. analyses ass HE, OR's: Hand washing/day: 10-19: 1.31 (0.71-2.36); 20-29: **5.77 (**2.53-13.2); >30: **13.1** (3.48-49.2) Glove wearing time/ per use 1-5 min: 1.6 (0.96-2.65); >5 min: **1.99** (1.01-49.2) Use of moisturizer times/day 1-2: 0.68 (0.33-1.44) 3-4: **0.27 (0.13-0.56**); 5-10: **0.13 (0.06-0.31)**; >10: **0.12 (0.05-0.30)** No ass. HE: department, duration of employment, working hrs., use of alcohol based hand rubs. No trend test for DRR
Ibler 2012 (53) Denmark	CS study of 2.269 HCW (physicians, nurses, nursing assistants and clinical assistants).	2269 (71%), ♀: 87% Age: 46.2 (10.3)	Self-rep daily handwashing, (freq. & duration of daily exp.), use of local disinfectants (freq.) and glove use (duration daily exp.)	Daily hand washes 0: 1%; 1-5: 24%; 6-10: 30%; 11-15: 18%; 16-20: 14%; >20: 2% Daily water exp. hours <0.5: 67%; 0.5-2: 12% 2-3: 7%; 3-5: 7%; >5: 7% Daily glove use hours: <0.5: 21%; 0.5-2: 50 %; 2-3: 18%; 3-5: 8% >5: 3%	HE: Self-rep last 12 months NOSQ 2002 standardized questionnaire. No clinical validation in study.	Sex, age, domestic exp. No adj. analyses. S. ass. HE with domestic exp. (handwashing, children <4 years old). No CI provid-ed.	21 % HE last 12 months *HE: trend with pos. **DRR** for ass.to freq. of handwashing, p<0.01. Odds HE (number hand washes): 0.6 (none), 0.21 (1-5), 0.24 (6-10), 0.31 (11-15), 0.28 (16-20), 0.44 (>20). No ass.to daily handwashing or glove exp. or to use of local disinfectants.

Table 8	Occupational exposures – outcome self-reported						
Author Year Country (ref.)	**Study Design**	**Study population Exposed/ controls (participation rate); Mean age and range**	**Exposure and Exposure Assessment**	**Exposure levels/duration**	**Outcome Diagnostic criteria**	**Covariates accounted for**	**Results PR/RR/OR**
Lan 2011 (93) Taiwan	CS study of 1132 Nurses from university hospital. Study 1.	1132 (93%) ♀: 99 % 31.6, 22-64 years	Years of work experience Work section (outpatient clinic, regular ward, special care unit)	32% >10 years work experience	HE based on diagnostic algorithm of symptoms validated in different study. Atopic eczema diagnosed according to Hanifin and Rajka criteria during the past year.	AD, sex (99% female) Housework hrs. pr. week HE ass. AD, no ass. housework.	PP, Adj. OR HE: Years' work experience: <5: 18.7%, 1; 5-10: 20.3%, 1.03 (0.71-1.50); >10: 27.3%, **1.52** (1.07-2.17) Work section NS
	Observational study of wet work exp. among 140 nurses from CS without atopic eczema from general wards with >1 year. experience. Study 2.	140 non-atopic working on general wards participating in study 1.	Hand washing water and detergents, use of alcohol rub, glove wearing. Observations of freq. and duration during a 4 hrs. morning shift.	During 4 hrs. times exp. (%), seconds exp. (%). Handwashing: >6 (36); >106 (33) Alcohol rub >9 (34),>62 (33) Gloves: >2 (21), >706 (24)	As above	Atopy (all without atopic eczema)	Adj. OR HE: Handwashing > 6 times: **3.02** (1.26-7.23) Alcohol rub >9 times: 0.62 (0.26-1.50) Gloves >2 times: 0.51 (0.17-1.48) Daily duration of exp. NS No DRR reported
Flyvholm 2007 (92) Denmark	CS study of Hospital employees. Questionnaire based.	1246 (65%), 1125 (58%) questions on HE). ♂126 (10%), ♀1016 (89%), unknown 104 (8%) Age: 42.9; 17-72 years	Self-rep jobs, daily hand-washing freq., daily/weekly use of hand disinfectants, use of protective gloves.	Handwashing >20 times/day:44.1 % of 1105; use of disinfectants: 54.3% of 1089; use of gloves: 46.8% of 669	HE: Self-rep HE last 12 months. Used NOSQ 2002 standardized questionnaire. No clinical validation in study.	Sex, age, AD, rhinitis, asthma HE more freq. atopic, females, <40 years No adj. analyses.	PP HE in job groups varied 7.9%-32.1%, mean 22.8%, highest for nursing (nurses and aids). PR* HE: Hand washing >20 times daily 1**.83*(**1.47-2.28); Disinfectants use daily/weekly 1.07* (0.85-1.34); Use of protective gloves **1.87*** (1.43-2.43) No DRR reported
HAIRDRESSERS							
Jung 2014 (91) Korea	CS questionnaire study of random sample 1% hairdressers in Korea.	1,054 (70%). Training status %: staff 27, masters 37, designers 36 ♀ 85.6 % 36.9 (10.4)	Self-rep. Exp. Hairdressing chemicals Training status Main work task (cutting, permanent wave, dying, washing, drying) Personal protective equipment	Main task % staff, designers, masters: Washing: 96.5; 2.0; 1.5. Cutting: 4.7; 43.4; 51.9 Permanent wave or dying: 24.5; 46.7; 28.8	HE based on self-rep. symptoms defined as redness & swelling, cracking or itching or blister formation with duration of >3 weeks No clinical validation.	Sex, age, civil status, smoking, alcohol, perceived health, personal protective equipment incl. adj. analyses.	PR CD (DS) 20.1%, Adj. OR ass.: training status vs. master: designer 1.22 NS, staff **2.70** (1.32-5.51) Main task vs. cutting: washing **2.03 (**1.22-3.37), other task NS. Exp. to chemicals 0.89 (0.53-1.49) No DRR reported

Table 8	Occupational exposures – outcome self-reported						
Author Year Country (ref.)	**Study Design**	**Study population Exposed/ controls (participation rate); Mean age and range**	**Exposure and Exposure Assessment**	**Exposure levels/duration**	**Outcome Diagnostic criteria**	**Covariates accounted for**	**Results PR/RR/OR**
WET WORK VARIOUS INDUSTRIES							
Mortz 2014 (47)	Prospective cohort study of young adults from general population 15 year after baseline study in 8'th grade. Questionnaire and clinical exam. at baseline and f-up.	Questionnaire 899 (60% of baseline, 75% of contacted at f-up). Clinical exam. 469 (31% of baseline, 39% of contacted at f-up) ♀ 56% 28-30 years.	Self-rep. exp. wet work, other work exp. (<½, ½-1, >2 h/day), freq. hand washing, hours of daily use of occlusive gloves. Also, self-rep. domestic exp. incl. minding of children<4 year., smoking habits.	Handwashing >20/day: 10.7%	HE Used NOSQ 2002 standardized questionnaire, with criteria self-rep. HE: history of eczema on hands, once for >2 weeks or relapsing or persistent. For subgroup clinical HE: inflammation with itching erythema, papules and/or vesicles and scaling at hand for ≥ 2 days. Patch test incl.	Atopy, gender, age, domestic exp., smoking.	Self-rep. current HE 7.1%, HE last year 14.3%. Current HE corresponded point prevalence of clinical HE 6.4% (n=30), 3% ACD, 76% some kind of ICD. Not clinical validation of questionnaire as clinical exam. performed with time interval up to .6 month after completion of questionnaire. *HE: unadjusted. trend with pos. **DRR** for ass.to frequency of handwashing, p=0.01. Odds HE (number hand washes): 0.15 (0-5), 0.14 (6-10), 0.14 (11-20), 0.37 (>20), Adj. analyses self-rep. HE last year (OR) ass. current wet work 1.7 (1.1-2.8)
Lazarov 2005 (90) Israel	CS study in population of 400 hydrotherapist completing training course 1998-2001, time for CS study not stated. Study based interview and postal questionnaires.	190 (48% of population, of 248 contacted, 77% of available population) 169 without pre-existing skin disease. ♀ 77% Age 61 % ≤ 39 years	Cumulative work hours in pools, calculated from self-rep. occupational history from telephone interview based questionnaire (product of working hours per week and number of years employment)	>10,000 cumulative work hours in pools: 20 % 59% worked as hydrotherapist at time of study. 15% had never worked as a hydrotherapist.	Self-rep skin disease with symptoms resembling CD after starting work as hydrotherapist. Symptoms incl. pruritus, burning &stinging, erythematous patches, xerotic skin affecting extremities, face and trunk and folds. No clinical validation.	Adj. analysis Pre-existing skin disease (11.9%), smoking (adj. OR 2.42 NS) No S. difference prevalence of AD in participants +/- symptoms.	Period prevalence development of self-rep. skin disease 45% (n=85) of all and 44% of workers without pre-existing skin disease, reported development of skin disease, with recurrence of CD ≥once in 59%. Adj. analysis, OR ≥ 10,000 cumulative hours exp. **2.81** (1.07–7.37) No DRR reported

Table 8	Occupational exposures – outcome self-reported						
Author Year Country (ref.)	**Study Design**	**Study population Exposed/ controls (participation rate); Mean age and range**	**Exposure and Exposure Assessment**	**Exposure levels/duration**	**Outcome Diagnostic criteria**	**Covariates accounted for**	**Results PR/RR/OR**
METALWORKING / FLUIDS AND OILS							
Mirabelli 2009(89) 10 European Countries	Pooled data from 2 multicenter population based f-up studies (ECHRS II and SAPLDIA 2). Baseline surveys in 1991 information previous eczema and skin-allergy. F-up surveys 1998/2002 information on work and prevalence of symptoms	676 (n.r), ♂:618 (91.4%) ♀: 58 (8.6%) 44.9, 28.3-72.1 years	Self-rep freq. in f-up questionnaire on metalworking tasks, manual work, metalwork, use of W-MWF, O-MWF and organic solvents / degreasing agents, when answering yes to a job involving metalworking during follow-up.	% working day(s) week <1, 1-3, 4-7: Hard Metals: 89, 5.5, 5.5; W- MWF: 80, 8.6, 10.9; O- MWF: 81.8, 77.3, 10.9; Organic solvents /degreasing agents 73.2, 14.5, 12.2	Self-rep ever itchy rash coming and going and present during last 12 months. No distinction between irritant and allergic reactions No clinical validation	Age, sex, history of eczema or skin allergy at baseline. Reported on atopy defined as respiratory atopy based on IgE measurements for sub-cohort, but not incl. adj. analyses.	12-month PP 10% **DRR** Adj. PP days working O- MWF, organic solvent and Hard metal. Day(s) week exp. compared ref <1: 1-3; 4-7: Adj. for age, sex: Hard Metal **1.52** (1.07-2.16) ,1.86 (0.96-3.62) O- MWF 0.89 (0.44-1.81) ,**1.16** (1.25-2.49); Organic solvents **1.84 (**1.14-2.97), **2.06** (1.21-3.50). Further adj. O-MWF or organic solvents for history of HE at baseline, manual work, use of respiratory/ventilation equipment, and organic solvents for O-MWF with similar results. O-MWF further adj. for W-MWF or organic solvents increased respectively decreased OR for 1-4 day(s) to **2.15** (1.35-3.44) and **1.43** (1.02-2.01)
CONSTRUCTION / CEMENT							
Avnstorp 1991(88) Denmark	Prospective 6-year cohort study (1981-1987) of workers in construction industry exp. to cement in period after reduction of content of water soluble chromate	67 (46%) still employed in industry with no clinical eczema at baseline. Age n.r Sex. n.r	Self-rep. freq. work processes involving cement exp. (concrete pouring, levelling, finishing, repairing). Also use of gloves, creams and handwashing. Cement had low content of water-soluble chromate during f-up.	No change in work processes or preventive measures of incl. workers.	Self-rep. episodes of HE previously/past/current lasting at least 2 weeks. Absence of ACD to cement verified by neg. patch test to chromate at baseline and f-up.	Allergy chromate	KIP self-rep. eczema 16.4%. No ass. duration cement exp. NS tendency ass. HE and concrete pouring (p=0.06) and other work task with cement exp. No ass. hand washing, glove or cream use. No DRR reported

Table 8	Occupational exposures – outcome self-reported						
Author Year Country (ref.)	**Study Design**	**Study population Exposed/ controls (participation rate); Mean age and range**	**Exposure and Exposure Assessment**	**Exposure levels/duration**	**Outcome Diagnostic criteria**	**Covariates accounted for**	**Results PR/RR/OR**
FIBRES							
Petersen 1991 (87) Denmark	CS study of construction workers exp. to mineral wool. Questionnaires based to members of working unions.	2654 (66%), different exp. levels. All ♂ 35, 15-69 years	Self-rep. MMMF exp. hrs. per month last year. Insulation workers and carpenters.	Hrs. per month exp. 0: ~ 20% 1-20: ~50% 21-149: ~ 20% 150-180: ~ 10%	Self-rep eczema when skin eruption/rash > once per week. Self-rep. stinging or itching skin > once per week. No clinical validation.	Age, smoking, organic solvents.	Exp. MMWF ass. irritative symptoms from skin (and eyes, respiratory system), 2/3 of highest exp. had symptoms. **DRR** in adj. analysis OR symptom each of 6 exp. categories: Itching skin: **1.89 (**1,39-1,55) Eczema: **1.29 (**1.21-1.38)
VARIOUS INDUSTRI /EXPOSURES							
Daftarian 2002(86) USA	CS study at a foam manufacturing facility of workers exp. to TDI and controls of non-production workers. Questionnaire, IgE and IgG antibodies to TDI, IgE antibodies to other allergens. Patch test TDI for subset of participants reporting skin problems	88/26 (39%) ♂ 31%/50% ♀ 69%/50% 39/42, 19-59/24-71 years	TDI and other chemicals (waxes and adhesives) used in foam-making or foam-repairing process. TDI measurements foam production: 104 individual TDI in breathing zone. 9 area samples. 3 measurements of +/- dermal exp. in demold area (removal of cushions after curing)	No individual or area samples above detection level. All 3 measurements of dermal exp.: + exp. No level given	Probable irritant reaction based on self-rep. dermal symptoms and neg. tests for allergy. Self-rep dermal symptoms (defined as dermatitis, eczema, or other red rash in the last 12 months). No clinical validation.	Allergy: No pos. patch test among 65% of eligible workers reporting skin symptoms One worker IgG pos. No adjusted analyses.	Production vs. non-production workers: dermal symptoms 40.9% vs. 15.4%, PR: 2.66 (1.14-16.32). No indication of type 1 or type 4 allergy to TDI. Concluded work related dermal symptoms represented an irritant reaction to TDI or reactions to other unidentified irritants / allergens. No DRR reported

Diagnoses: ACD: Allergic contact dermatitis; AD: Atopic dermatitis; CD: contact dermatitis; HE: Hand eczema;
Exposures and confounders: exp: exposure; MWF: Metal working fluids; W-MWF: water-based MWF=soluble MWF; O-MWF: oil-based MWF=neat/insoluble MWF
HCW: Healthcare workers
Study characteristics: adj: adjusted; ass: association; CC: case control study; CS: cross sectional; DRR: dose-response relation; exam: examination; f-up: follow-up; freq: frequent; hrs.: hours; incl: included; neg: negative; n.r: not reported; NS: non-significant; OR: odds ratio; PP: Prevalence proportion; PR: Prevalence ratio; S: significant;; self-reported: self-rep.; vs.: versus;
* Calculated from data I article

9.1.4 Table 9 Studies on prognostic factors for ICD

Table 9	Studies on prognostic factors for ICD						
Author Year Country (ref.)	**Study Design**	**Study population Exposed/ controls (participation rate); Mean age and range**	**Exposure and occupational variables**	**Exposure levels/duration** **Occupational consequences**	**Prognostic outcome** **Diagnostic criteria**	**Covariates accounted for**	**Results PR/RR/OR**
Vester 2012(107) Denmark	Prospective cohort study of outcome in pt. with clinically verified OCD of the hands from food-related jobs 0.3-10 year. after diagnosis. Focus on protein contact dermatitis.	258 (69%) 178 included ♂: 30% Age 17-65 Subgroups OCD: Protein CD: 28 % (50) ICD: 63.5% (113) ACD, CU, multiple: 8.5% (15)	Work-related consequences Self-rep. job changes due to skin problems Sick leave	Job change due to skin problems Protein CD: 62% (31) ICD~others: 43% (52) Sick leave>3 weeks: Protein CD:21% (10) ICD~others:10% (12)	Self-rep. improvement in sub-groups of OCD of hands. At baseline clinical diagnoses of subgroups of HE, incl. ICD. At f-up improvement and work-related consequences reported in 2 groups, protein CD and others ~ICD (88% ICD)		84% improved when job change with no difference between diagnostic groups comparing protein CD with others (ICD 88%).
Malkonen 2009(102) Finland	Prospective cohort study of patients diagnosed with OSD incl. ICD at FIOH. Questionnaire 6 month after diagnosis in 1994-2001.	OSD 1048 (89%) ♂ 476; ♀: 572 41.7(10.8) years. Subgroup with ICD: 363	Self-rep. occupational change, change of work task Various exp. not specified. Various occupations mainly food related, dental personnel, farmers, machinery mechanics, hairdressers, machinists and healthcare workers.	ICD and changed work tasks: 19 % job/occupation: 12% loss of job: 13% ICD, no changes in work: 47%	Self-rep. continuation or healing of ICD 6 month after initial clinical diagnosis, incl. patch test and prick test. Baseline diagnostic criteria: i) exp. to irritants at work, ii) development and location correlating with exp., iii) no relevant work-related allergy detected.	Age, sex, atopy, work-related contact allergies., occupation	23% of ICD healed in 6 months. Adj. analysis for continuation of OCD, OR: Diagnosis ACD ref. ICD: 1.0 No work changes: **2.7** (1.9-3.8), Food related occupation**: 1.8** (1.1-3.1), other occupational groups NS. Skin atopy: 1.4 NS Respiratory atopy: **1.8** (1.1-3.1) Age >45 year: **2.3** (1.7-3.3) Male sex: **1.6** (1.0-2.3)

Table 9	Studies on prognostic factors for ICD						
Author Year Country (ref.)	**Study Design**	**Study population Exposed/ controls (participation rate); Mean age and range**	**Exposure and occupational variables**	**Exposure levels/duration Occupational consequences**	**Prognostic outcome Diagnostic criteria**	**Covariates accounted for**	**Results PR/RR/OR**
Malkonen 2010 (103) Finland	Prospective cohort study of medical and occupational outcome in patients with OCD of the hands 7-14 (mean 10.5) years after diagnosis at FIOH in 1994-2001, who participated in follow-up study 6 month after diagnosis.	605 (80.1%) OCD ACD: n=354 ICD: n=251 ♂ 45% ♂ 42.9 (10.5) years ♀ 42.2 (11.1) years Baseline study population subpopulation of (102)	Prognostic factors for continuous OCD of hands Duration of OCD Change of occupation Type of occupation Various exp. not specified, as (102) .	ICD, work changes work tasks or job: 55 % occupation: 35% loss of job: 18% ICD, no work changes: 8% Duration of OCD prior to diagnosis: Mean: 4.82 year 0-1 year: 30% 1-2 years: 18% 2-5 years: 21% 5-10 years: 14% >10 years: 14%	Self-rep healing of baseline OCD (incl. ICD) defined as no HE in last 12 months. Baseline diagnoses as defined in (102)	Age, sex, skin atopy, work related contact allergy.	OCD healed: 40%. No diff. ACD 43% & ICD 35%. *27% with continuous OHE had symptoms every week.* Adj. analyses continuous OCD ass. OR Duration of OCD prior to diagnosis, years, (reference<1 year,) 1-2 years: **3.1** (1.8-5.2); 2-5 years: **1.9** (1.2-3.1); 5-10 years: **2.6** (1.4-4.6); >10 years: **4.6** (2.4-8.7). No change of occupation **1.6** (1.03-2.34) Skin atopy: **1.9** (1.1-3.2) Respiratory atopy: **2.7** (1.4-4.9) No S ass. OHE and type of occupation, work-related contact allergy, age or sex.
Cvetkovski 2006 (108) Denmark	Prospective cohort study of outcome in pt. with recognized OCD of the hands reported by dermatologist to the Danish National Board of Industrial Injuries 1 year after diagnosis.	564 (91 % of baseline participants) with OCD ♂**: 32**% Age: reported 5 age-groups from 18->50 Subgroups OCD hands: ICD: 61% ACD: 20% ICD+ACD: 10% ICD+CU: 5% CU: 5%	Self-rep. job-change during f-up. Socioeconomic status Recorded occupation at baseline. Disease duration	Job change f-up: 48% Socioeconomic status: Student, trainee: 19% High/medium: 15% Basic level: 42% Lowest level: 24% High-medium socioeconomic status associated favourable prognosis for prolonged sick leave.	Aggravation, persistence or improvement of self-rep. severity of HE and subgroups incl. ICD. Self-rep. baseline and f-up severity last 12 months on visual analog scale converted to 3 severity groups: 1.No or minimal 2. Mild to moderate 3. Severe At baseline, also clinical scoring of severity by dermatologist.	Age Sex AD Occupation Depression	Overall improvement 41 %, varied from 11-67 % in the different job-groups. Overall 25% aggravated or persistent severe HE. No association between job-change and change in severity Adj. analyses aggravated or persistent HE (RR): AD ass. worse prognosis**: 1.53** (1.1-2.2) Age >25 ass. worse prognosis No association diagnostic group (irritant or allergic), sex, disease duration or occupation, tendency better prognosis better prognosis high-medium level socioeconomic status 0.56 (0.3-1.0) Risk of job loss ass. dermatologist rated severe OCD at baseline RR **14.0.**

Table 9	Studies on prognostic factors for ICD						
Author Year Country (ref.)	**Study Design**	**Study population Exposed/ controls (participation rate); Mean age and range**	**Exposure and occupational variables**	**Exposure levels/duration Occupational consequences**	**Prognostic outcome Diagnostic criteria**	**Covariates accounted for**	**Results PR/RR/OR**
Jungbauer 2004 (106) The Netherlands	Prospective cohort study of outcome in patients clinically diagnosed with ICD in dermatological department 5 years. after diagnosis.	124 (72 %) ♂**: 46**% Age: 42	3 levels current exposure skin irritants, score based on self-rep. freq. handwashing, duration wet hands, freq. exp. soaps and detergent. Self-rep. preventive measures (gloves, emollients, adjustments of exposure to irritants)	Current exposure: Low: 48% Medium: 9% High: 42% 57% changed occupation.	Self –reported disease severity (score incl., ADL´, freq. of relapses, freq. of visiting dermatologist and use of topical corticosteroids) Baseline clinical diagnosis.	Excluded patients with ACD and patients with primary AD.	Severity scores 5 years after diagnosis: medium 50%, high in 32% No significant association between severity of HE and parameters for exposure, sex or occupation. (analyses or statistics not specified) 25 % reported loss of workdays because of dermatitis during f-up, mean duration 68 days per year.
Adisesh 2002(101) UK	Prospective study of consequences of reported OCD to surveillance scheme. Questionnaire by consultant physicians (dermatologist and occupational) with mean follow-up of 164 and 353 days.	Random sample of ~100 ICD, 100 ACD, 100 mixed from each group of specialists. Participation 510 (71%), 287 (83%) dermatologist, 225 (60%) occupational physician. ♂**:** 59.2% Age ♂**/** ♀**:** 41.5/33.4 15-75/15—62 years.	Exposure duration (years.) prior to diagnosis Notification of cases as OCD (medicolegal assessment)	Exp. duration: <½ year: 17 % ½-3 years: 22% 3-10 years: 27% >10 years: 18% Unknown: 17%	Time off work (sick leave and/or unemployment) Improvement clinical condition during f-up evaluated by physician (available for 313) OCD (ICD, ACD, mixed) diagnosed clinically, patch test of 61%.	Time of work adj. age, sex, atopy, diagnosis. Non-improvement no adj. analyses.	Time off work: PP 21% total, 35%<3 weeks, 11% >1 year. ICD 16%, ACD 26%, mixed 20% Adj. analyses time off work, OR ACD vs. ICD/mixed: **1.8** (1.1-2.8) Age/10 year: **1.3** (1.1-1.5) Notification of OCD: **4.4** (2.2-8.9) No ass.to duration of exposure, sex or atopy. Non-improvement: PP 15.7% total, 22.4% (dermatologist), 8.1% (occupational phys.) F-up time longer when non-improvement. Overall no ass. age or atopy. Age ≤45 years atopic vs. non-atopic 25% vs. 13%, p=0.04 Age >45 years, no significant association atopy. Mean duration of exposure non-improvement vs. improvement All OCD: 7.6 years. vs. 5.3 years. (NS) Non-atopic: 9.1 years vs. 5.3 years. (p=0.03). Type of OCD not related to improvement

Table 9	Studies on prognostic factors for ICD						
Author Year Country (ref.)	**Study Design**	**Study population Exposed/ controls (participation rate); Mean age and range**	**Exposure and occupational variables**	**Exposure levels/duration Occupational consequences**	**Prognostic outcome Diagnostic criteria**	**Covariates accounted for**	**Results PR/RR/OR**
Nielsen 1996(96) Denmark	Prospective 2 years cohort study 1989-91 of female cleaners at 271 public institutions.	1011 (88%) at follow-up. Age n.r. (baseline CS study table 8)	Self-rep employment status f-up: cleaners, non-cleaning work, unemployed, retired.	Continuous cleaning: ~ 79 %; non-cleaning work: ~ 7%; unemployed: ~4%; retired: ~4%;	Prognosis at f-up of self-rep skin symptoms reported at baseline.	Adj. age, sex (all females)	Tendency higher prevalence of skin symptoms at baseline among cleaners leaving their job. Leaving cleaning vs. continuous cleaning: Adj. analysis better prognosis baseline symptoms, OR: Red and rough skin: **0.3 (0.2-06);** cracks**: 0.4 (0.2-0.7);** vesicles: 0.6 (0.2-1.9); itching: 0.8 (0.4-1.4)
Shah 1996 (105) UK	Prospective cohort study of self-rep. prognosis of OCD of the hands in metalworkers 1-5 years after clinical diagnosis Clinic in 1988-1993 at Contact Dermatitis	OHE: 51 (80%) ICD: 31% (16), ACD: 53% (27), AD 16% (8) Baseline: ♂**:** 91% Age: 45.7 (21-67)	Self-rep. continuous exp. cutting oil.	43 % continuous exp. 57 % not exp., majority at least 2 years 55% of non-exposed unemployed or retired.	Self-rep. continuous symptoms of HE. Baseline clinical diagnoses: ACD: pos. patch test relevant allergen. ICD: Irritant factors evaluated as important. AD: history of atopy, no relevant allergy.	AD incl. as subgroup of OHE. No further adjustment for atopy.	Continuous symptoms PP total 82%, no S difference diagnoses, (88% ICD, 78% ACD, 88% AD) Continuous exp. vs. non-exposed Continuous symptoms: 86% vs 79%, RR* 1.1 NS Symptoms last 3 months: 68% vs 66%, NS
Rosen RH 1993 (100) Australia	Prospective 1-5 years cohort study of patients with OCD diagnosed at Occupational and Contact dermatitis clinic.	OCD: 334 (59%) ICD: 58 % (195) ACD: 42% (139) Sex: n.r. Age: n.r.	Self-rep. change of occupation and change of work tasks. 4 main industries/occupations: Hairdresser Food Construction Medical	OCD, changed industry: 37% (n=122) Hairdressers: 47% Food industry: 39% OCD, same industry, changed work tasks: 24% (n=51) Numbers in industries n.r.	Healing rate, improvement rate (healed or better) based on self-rep. status of healing in 5 outcomes (healed, better, static, worse or crippled). Baseline all clinical diagnosis incl. patch test.	Atopy (dermal or respiratory). No adj. analyses. Analyse for bias of non-participation (incl. sex, age, occupation and more)	Overall improvement rate 70% (~ 1/ 3 healed, 1/ 3 better, 1/ 4 no significant change, 1/ 12 had deteriorated) ACD vs. ICD: No S difference prognostic outcome overall or in each industry Construction industry reported poor prognosis, improvement rate only 45% **(p<0.02**), lover improvement rate for allergies found in construction industry. Change of occupation vs. same industry Healed: 43% vs. 28%; **RR* 1.6** (1.2-2.1) Improvement: 76% vs. 67%, RR* 1.14 (1.0-1.3) Change of work tasks vs. same work tasks: Healed: 43% vs. 24%; **RR*1.8** (1.2-2.8) Improvement: 82% vs. 61%, **RR* 1.4** (1.1-1.6) Improvement atopic vs. non-atopic 62% vs. 79%, p<0.01

Table 9	Studies on prognostic factors for ICD						
Author Year Country (ref.)	**Study Design**	**Study population Exposed/ controls (participation rate); Mean age and range**	**Exposure and occupational variables**	**Exposure levels/duration Occupational consequences**	**Prognostic outcome Diagnostic criteria**	**Covariates accounted for**	**Results PR/RR/OR**
Chia 1991 (104) Singapore	Prospective 1 year. cohort study of patients with OCD diagnosed at Occupational and Contact dermatitis clinic.	OCD 112 (87 %) ACD 28% (31) ICD 73% (81) ♂ 68% Age groups years: <20: 5%, 20-29: 45%; 30-39:32%; ≥40: 18%	Prognostic factors for continuous OHE recorded at baseline: Occupation Duration of employment/ exposure Type of exposure, which caused OCD	ICD duration exposure, yeas: <1: 43%,1-<3: 31%; ≥3: 26% ICD avoid exposure: Oil/coolants: 46% (11) Solvents/flux: 52% (12)	Healing or persistence of OCE, Clinical assessed in 41%, interview- based in 59%. Baseline clinical diagnoses, criteria ICD incl. neg. patch-test, relevant exposure. Only incl. patients with single diagnosis.	Sex, age, ethnicity, ACD No adj. analyses.	OCD healed in 72 % of cases. No difference between ACD and ICD ICD: In stratified analyses. No difference in prognosis for age, sex, ethnicity, duration of exposure. Prognosis for patients with ICD from exposure to oil/coolants and solvents did not depend on continued or avoidance of exposure.
Lindemayr 1984 (99) Austria La. German.	Retrospective clinical record based cohort study of hairdressers with OCD diagnosed at Occupational and Contact dermatitis clinic. Observation time varied 0.3-2 year., mean 15 months.	OCD 215 (87 %) ACD 71% (154) ICD/non-ACD 29% (61) ♀ 97% Age n.r.	Change of occupation Detailed listing of all type of chemicals used at baseline, but no description of wet work.	62% discontinued hairdressing, similar for ACD and ICD.	Healing of OCD (ACD, ICD), assessed clinical. Baseline clinical diagnosis incl. patch-test. Non-allergic ~ICD incl. workers, who had positive patch-test to work-substances, but neg. to European Standard and hairdressing series.	Atopy in 10% No adj. analyses.	Healing in 38% who continued as hairdressers: ACD: in 19% (n=11) of all, 32% of pt. with information, missing 41%. ICD: in 46% (n=11) of all, 58% of pt. with information, missing 21%. Healing in 62% who discontinued as hairdressers: ACD in 60% (n=58) of all, 70% of pt. with information, missing 14% ICD: in 68% (n=25) of all, 78% of pt. with information, missing 14% No statistical analyses
Ketczkes 1983 (98)UK	Prospective cohort study of outcome in patients clinically diagnosed with ICD in dermatological department 1-16 years. after diagnosis 1966-82.	188 (41%), all ICD. Age n.r. Sex n.r.	Self-rep. change of occupation. Occupations at baseline not reported, only for subgroup of housewife/part –time cleaners.	49% (64) changed occupation. 24% (46) were housewife/part-time cleaners.	Self-rep. healing or active ICD of the hands. Healing defined as no active (continuous or periodic) ICD. ICD: diagnosed clinically at baseline, all neg. patch tests. Does not specify if ICD occupational at baseline.	Excluded patients with history of AD or psoriasis.	PP (95% CI*) active ICD: 69 (62-76*) %, healed 31 (24-38) % Healing of ICD when change of occupation vs. same occupation. PP 33% vs. 30%, PR* 1.10 (0.7-1.7)

Diagnoses: ACD: Allergic contact dermatitis; AD: Atopic dermatitis; CU: Contact urticaria; HE: Hand eczema; CD: Contact dermatitis; ICD: Irritant contact dermatitis; OCD: Occupational contact dermatitis; OSD: Occupational skin disease
Exposures and confounders: exp: exposure;

Study characteristics: ADL: Activities of daily living; adj: adjusted; ass: association; CS: cross sectional; f-up: follow-up; freq: frequent; incl: included; neg: negative; n.r: not reported; NS: non-significant; OR: odds ratio; PP: Prevalence proportion; RR: relative risk; S: significant; self-rep: self-reported; vs.: versus;
* Calculated from data I article

9.1.5 Table 10 Quality assessment of presented studies

Table 10	Quality assessment of 45 studies, 50 papers presenting analyses of association ICD or prognosis of ICD in relation to work exposures										
Author	**Study design**	**Dimension**	**Response rate**	**Exposure source**	**Exposure measure**	**Outcome source**	**Outcome measure**	**Confounder control**	**Total Score**	**Grading of study**	**Work Exposure**
Table 6											
Held, 2001 (71)	1	0	1	0	0	1	1	1	5	3	HCW
Stingeni, 1995 (70)	0	1	1	0	0	1	1	0	4	4	HCW
Guo, 1994 (69)	0	0	1	0	0	1	1	0	3	3	Hairdressers
Teo, 2009 (62)	0	0	1	0	0	1	1	1	4	3	Food industry
Tacke, 1995 (68)	1	1	n.r	1	0	0	1	0	4	3	Food industry
Kavli 1987 (67)	0	0	1	1	0	1	1	0	4	4	Food industry
Stingeni, 1996 (66)	0	1	1	0	0	1	1	0	4	4	Gloves
de Boer 1989, (65)	0	1	n.r	0	0	1	1	1	4	3	Metal work
Jee, 1986 (64)	0	0	n.r	1	1	1	1	0	4	3	Metal work
Fischer, 1985 (72)	0	1	1	1	0	0	1	0	4	4	Metal work
Kieć-Świerczyńska, 2000 (63)	0	1	n.r	1	1	1	1	0	5	2	Mineral fibres
Table 7											
Callahan, 2013 (85)	1	0	1	0	0	1	0	1	4	2	HCW
Bauer, 2001 (84)	1	0	1	0	0	1	0	1	4	3	Food industry
Bauer, 1998 (83)	1	0	1	0	0	1	0	0	3	3	Bakers
Uter, 1998-1999 (78, 79, 81, 82)	1	1	1	0	0	1	0	1	4	2	Hairdressers
Weistenhofer, 2015 (77)	0	1	1	1	0	1	0	1	5	2	Gloves
Vermeulen, 2001(80)	0	0	1	0	0	1	0	1	3	3	Wet work
				1					4		Gloves
Berndt, 2000 (76)	1	0	1	1	1	1	0	1	6	2	Metal work
Goh,1994 (75)	0	0	n.r	1	0	1	0	1	3	4	Metal work
Apfelbacher, 2010 (74)	1	0	1	0	0	0	0	1	3	3	Metal work
Chou, 2004 (73)	0	0	n.r.	1	0	1	0	0	2	3	CS_2, H_2SO_4
Table 8											
Mirabelli, 2012 (97),	0	1	n.r.	0	0	0	0	0	1	4	Cleaners
Nielsen, 1996 (96)	0	1	0	0	0	0	0	0	1	4	Cleaners
Visser, 2013 (95)	1	1	1	0	1	0	0	0	4	3	HCW
Visser, 2013 (40)	1	1	1	0	1	0	0	1	5	3	HCW
Lee, 2013 (94)	0	1	1	0	0	0	0	1	3	3	HCW
Ibler, 2012 (53)	0	1	1	0	0	0	0	0	2	4	HCW/

Table 10	Quality assessment of 45 studies, 50 papers presenting analyses of association ICD or prognosis of ICD in relation to work exposures										
Author	**Study design**	**Dimension**	**Response rate**	**Exposure source**	**Exposure measure**	**Outcome source**	**Outcome measure**	**Confounder control**	**Total Score**	**Grading of study**	**Work Exposure**
Lan, 2011 (93) study 1	0	1	1	0	1	0	0	1	4	3	HCW
Lan, 2011 (93) study 2		0		1						2	
Flyvholm, 2007 (92)	0	1	1	0	0	0	0	0	2	4	HCW
Jung, 2014 (91)	0	1	1	0	0	0	0	0	2	4	Hairdressers
Mortz, 2014(47)	1	1	1	0	0	0	0	1	4	3	Wet work
Lazarov, 2005 (90)	0	1	1	0	0	0	0	0	2	4	Wet work
Mirabelli, 2009(89)	1	0	n.r	0	0	0	0	0	1	3	MWF
Avnstorp, 1991(88)	1	0	0	0	0	0	0	0	1	4	Cement
Petersen 1991 (87)	0	1	1	0	0	0	0	0	2	3	Mineral fibres
Daftarian, 2002 (86)	0	0	0	1	1	0	0	0	2	4	TDI
Table 9 Prognosis											
Vester, 2012 (107)	1	1	1	0	n.a.	0	1	0	4	3	Various
Malkonen, 2010 (103)	1	1	1	0	n.a.	0	1	1	5	2	Various
Malkonen 2009 (102)	1	1	1	0	n.a	0	1	1	5	2	Various
Cvetkovski, 2006 (108)	1	1	1	0	n.a.	0	1	1	5	2	Various
Jungbauer, 2004 (106)	1	1	1	0	n.a	0	1	0	4	4	Various
Adisesh, 2002 (101)	1	1	1	0	n.a	1	0	1	5	3	Various
Nielsen, 1996 (96)	1	1	1	0	n.a	0	0	0	3	3	Cleaners
Shah, 1996 (105)	1	0	1	0	n.a.	0	1	0	3	4	Metal-workers
Rosen RH, 1993 (100)	1	1	1	0	n.a.	0	1	1	5	3	Various
Chia, 1991(104)	1	1	1	0	n.a.	0	1	0	4	3	Various
Lindemayr, 1984 (99)	0	0	1	0	n.a.	1	0	0	2	4	Hairdressers
Ketczkes, 1983 (98)	1	1	0	0	n.a.	0	1	1	3	4	Various

n.r: not reported;n.a: not applicable

Grading of study. 1: high; 2: medium-high; 3: medium; 4: low; 5: un-acceptable

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11 Appendix

11.1.1 Search Strategy

Review of causes of irritative (toxic) contact eczema after occupational exposure to irritative influences of the skin

PubMed, search strategy, table and search string. Date of search October 29th, 2015

Outcome		**Irritative skin exposure**		**Work-relation**	**References**
#1 contact dermatitis[MH] OR hand dermatoses[MH] OR eczema*[TW] OR dermatitis[TW]	**AND**	**#4** irritants[MH] OR irritative[TW] OR irritant*[TW] OR phototoxic*[TW] OR wet work[TW]OR detergents[MH] OR detergent*[TW] OR cutting fluid*[TW] OR "Industrial Oils/adverse effects"[Mesh]	**AND**	**#5** occupational exposure[MH OR occupational diseases[MH] OR occupational group[MH] OR occupation*[TW] OR industry[MH] OR industry[TW]	**#9** **1623**
#2 occupational dermatitis[MH] OR occupational dermatitis[TW]	**AND**	**#4** irritants[MH] OR irritative[TW] OR irritant*[TW] OR phototoxic*[TW] OR wet work[TW]OR detergents[MH] OR detergent*[TW] OR cutting fluid*[TW] OR "Industrial Oils/adverse effects"[Mesh]			**#14** **1114**
#3 irritant dermatitis[MH] OR Phototoxic dermatitis [MH] OR irritant dermatitis[TW] OR			**AND**	**#5** occupational exposure[MH OR occupational diseases[MH] OR occupational group[MH] OR occupation*[TW] OR	**#11** **673**

irritant contact dermatitis[TW]				industry[MH] OR industry[TW]	
#6 english[LA] OR german[LA] OR danish				**(#9 OR #10 OR #11) AND #6**	**#12** **1465**
#7 case reports[PT]				**#12 NOT #7**	**#13** **1203**
#8 Review[PT]				**#13 NOT #8** (*original articles without reviews, no date limits*)	**#14** **959**
				#13 AND #8 (*reviews without cases, no date limits*)	**#15** **244**
				#12 AND #7 AND #8 (*reviews with cases, no date limits*)	**#16** **12**

#1	*contact dermatitis[MH] OR hand dermatoses[MH] OR eczema*[TW] OR dermatitis [TW]*
#2	*occupational dermatitis[MH] OR occupational dermatitis[TW]*
#3	*irritant dermatitis[MH] OR Phototoxic dermatitis [MH] OR irritant dermatitis[TW] OR irritant contact dermatitis[TW]*
#4	*irritants[MH] OR irritative[TW] OR irritant*[TW] OR phototoxic*[TW] OR wet work[TW]OR detergents[MH] OR detergent*[TW] OR cutting fluid*[TW] OR "Industrial Oils/adverse effects"[Mesh]*
#5	*occupational exposure[MH OR occupational diseases[MH] OR occupational group[MH] OR occupation*[TW] OR industry[MH] OR industry[TW]*
#6	*english[LA] OR german[LA] OR danish[LA]*
#7	*case reports[PT]*
#8	*Review[PT]*
#9	*#1 AND #4 AND #5*
#10	*#2 AND #4*
#11	*#3 AND #5*
#12	*(#9 OR #10 OR #11) AND #6*

#13 #12 NOT #7

#14 #13 NOT #8

#15 #13 AND #8

#16 #12 AND #7 AND #8

Embase, search strategy, table and search string. Date of search October 29th, 2015

Outcome		**Irritative skin exposure**		**Work-relation**	**References**
1 exp * hand disease/ 2 exp *contact dermatitis/ 3 (hand adj3 dermatoses) tw 4 (hand adj3 dermatosis).tw. 5 exp 'eczema/ 6 exp *dermatitis **7: 1 or 2 or 3 or 4 or 5 or 6**	**AND**	15 irritant agent/ 16 irritant*.tw. 17 irritative.tw. 18 Phototoxic.tw. 19 (wet adj3 work).tw. 20 Dertergent/ 21 Oil/ae[Adverse Drug Reaction] 22 "industrial oil*2.tw 23 detergent.tw. 24 "cutting fluid*2".tw. **25 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24**	**AND**	26 *occupational exposure/ 27 exp *occupational disease/ 28 exp *named groups by occupation/ 29 exp *industry/ 30 industr*.tw. 31 occupation*.tw. **32 26 or 27 or 28 or 29 or 30 or 31**	**(33)** **1012**
8 occupational eczema/ 9 (occupational adj3 dermatitis).tw. **10: 8 or 9**	**AND**	15 irritant agent/ 16 irritant*.tw. 17 irritative.tw. 18 Phototoxic.tw. 19 (wet adj3 work).tw. 20 Dertergent/ 21 Oil/ae[Adverse Drug Reaction] 22 "industrial oil*2.tw 23 detergent.tw. 24 "cutting fluid*2".tw. **25: 15 or 16 or 17 or 18 or 19 or 20 21 or 22 or 23 or 24**			**(34)** **839**
11 irritant dermati-			**AND**	26 *occupational expo-	**(35)**

tis/ 12 (irritatant adj3 dermatitis).tw. 13 (phototoxic adj3 dermati-tis).tw. **14: 11 or 12 or 13**				sure/ 27 exp *occupational disease/ 28 exp *named groups by occupation/ 29 exp *industry/ 30 industr*.tw. 31 occupation*.tw. **32: 26 or 27 or 28 or 29 or 30 or 31**	**819**
				33 or 34 or 35	**(36)** **1626**
				Limits Danish or English or German	**(37)** **1371**
38 case report/				**37 not 38**	**(39)** **1232**
40 review/				**39 not 40** (*original articles without re-views, no date limits*)	**(41)** **1001**
				39 and 40 (*reviews without cases, no date limits*)	**(42)** **231**
				37 and 38 and 40 (*reviews with cases, no date limits*)	**(43)** **6**

1 exp * hand disease/
2 exp *contact dermatitis/
3 (hand adj3 dermatoses) tw
4 (hand adj3 dermatosis).tw.
5 exp 'eczema/
6 exp *dermatitis

7	1 or 2 or 3 or 4 or 5 or 6
8	occupational eczema/
9	(occupational adj3 dermatitis).tw.
10	8 or 9
11	irritant dermatitis/
12	(irritatant adj3 dermatitis).tw.
13	13 (phototoxic adj3 dermatitis).tw.
14	11 or 12 or 13
15	irritant agent/
16	irritant*.tw.
17	irritative.tw.
18	Phototoxic.tw.
19	(wet adj3 work).tw
20	Dertergent/
21	Oil/ae[Adverse Drug Reaction]
22	”industrial oil*2.tw
23	detergent.tw.
24	24 ”cutting fluid*2”.tw.
25	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26	*occupational exposure/
27	exp *occupational disease/
28	exp *named groups by
29	exp *industry/
30	industr*.tw.
31	occupation*.tw.
32	26 or 27 or 28 or 29 or 30 or 31
33	7 and 25 and 32
34	10 and 25
35	14 and 32
36	33 or 34 or 35
37	Limit 36 to (danish or English or german)
38	case report/
39	37 not 38
40	review/
41	39 not 40
42	39 and 40
43	37 and 38 and 40

Web of Science, search strategy, table, search string. Date of search November 5'th 2015.

Outcome		**Irritative skin exposure**		**Work-relation**	**References**
#1 TS=(contact NEAR/3 dermatitis) #2 TS=(hand NEAR/3 dermato-ses) #3 TS=(hand NEAR/3 dermato-sis) #4 Topic: (eczema*) OR topic: (dermatitis) **#5= #1 or #2 or #3 or #4**	**AND**	#8 TS= (irritant*) OR TS= (irrita-tive) OR TS= (phototoxic*) OR TS=(detergent*) #9 TS=(wet NEAR/3 work) OR TS=(cutting NEAR/3 fluid*) OR TS=(industrial NEAR/3 oil SAME adverse) **#10= #8 or #9**	**AND**	**#11** TS=(occupational NEAR/3 exposure) OR TS=(occupational NEAR/disease*) OR TS=(occu-pation*) OR TS=(industry)	**#12** **815**
#6 TS=(occupational NEAR/3 dermatitis)	**AND**	#8 topic: (irri-tant*) OR topic: (irritative) OR topic: (phototox-ic*) OR topic (de-tergent*) #9 TS=(wet NEAR/3 work) OR TS=(cutting NEAR/3 fluid*) OR TS=(industrial NEAR/3 oil SAME adverse) **#10= #8 or #9**			**#13** **402**
#7 TS=(irritant NEAR/3 dermatits) OR TS=((phototoxic NEAR/3 dermatitis) OR TS=(irritant			**AND**	**#11** TS=(occupational NEAR/3 exposure) OR TS=(occupational NEAR/disease*) OR TS=(occu-pation*) OR TS=(industry)	**#14** **521**

contact dermatitis)					
				#12 OR #13 OR #14	**#15** **815**
				#15 AND LA=(English OR German)	**#16** **763**
				#16 NOT DT=(review)	**#17** **666**
				#16 AND DT=(review)	**#18** **97**
				#16 NOT DT=(review) Refined by: [excluding] **DOCUMENT TYPES:**(PROCEEDINGS PAPER OR MEETING ABSTRACT OR HARDWARE REVIEW OR NOTE OR EDITORIAL MATERIAL OR LETTER)	**#19** **587**

OSH-UPDATE, Databases HSELINE, NIOSHTIC, CISDOC and RILOSH. Search strategy, table, search string. No limits have been added

Date of search November 3'th 2015

Outcome		**Irritative skin exposure**		**Work-relation**	**References**
#1 GW{contact dermatitis} OR GW{eczema*} OR GW{dermatitis} OR GW{hand dermatoses}		**#4** GW{irritant*} OR GW{irritative} OR GW{phototoxic*} OR GW{wet work} OR GW{detergent*} OR GW{cutting fluid} OR GW{industrial oil**}**		**#5** GW{occupational exposure} OR GW{occupational disease*} OR GW{industry}	**#6:** **1646**
#2 GW{occupational dermatitis}	AND	**#4** GW{irritant*} OR GW{irritative} OR GW{phototoxic*} OR GW{wet work} OR GW{detergent*} OR GW{cutting fluid} OR GW{industrial oil}			**#7** **557**
#3 GW{irritant dermatitis} OR GW{phototoxic dermatitis}OR GW{irritant contact dermatitis}			AND	**#5** GW{occupational exposure} OR GW{occupational disease*} OR GW{industry**}**	**#8** **354**
				#6 OR #7 OR #8	**#9** **1877**
#10 DC{OUHSEL} OR DC{OUCISD} OR DC{OUNIOC} OR DC{OURILO}				**#9 AND #10**	**#11** **1406**

Search string.

Step: Hits: Strategy:

#1 13807 GW{contact dermatitis} OR GW{eczema*} OR GW{dermatitis} OR GW{hand dermatoses}

#2 1999 GW{occupational dermatitis}

#3 791 GW{irritant dermatitis} OR GW{phototoxic dermatitis} OR GW{irritant contact dermatitis}

#4 17556 GW{irritant*} OR GW{irritative} OR GW{phototoxic*} OR GW{wet work} OR GW{detergent*} OR GW{cutting fluid} OR GW{industrial oil}

#5 144103 GW{occupational exposure} OR GW{occupational disease*} OR GW{industry}

#6 1646 #1 AND #4 AND #5

#7 557 #2 AND #4

#8 354 #3 AND #5

#9 1877 #6 OR #7 OR #8

#10 685428 DC{OUHSEL} OR DC{OUCISD} OR DC{OUNIOC} OR DC{OURILO}

#11 **1406** #9 AND #10

All databases, original papers

Pubmed	PubMed 1959-2015	959
	≥ 1980	862
	Dublets	3
	Titles database from pubmed	**859**
Embase	1959-2015	1001
	≥1980	915
	Dublets Embase	16
	Dublets PubMed	512
	Conference abstracts	169

	Titles database from Embase	**218**
Web of Science (WOS)	1934-2015	587
	≥1980	585
	Dublets Pubmed and Embase	428
	Case reports	50
	Titles database from WOS	**107**
OSH-UPDATE	1922-2011	1406
	≥1980	1113
	Dublets OSH-UPDATE	108
	Dublets other databases	248
	Language	90
	Case reports	170
	Conference abstracts, pamphlets, evaluation reports	260
	Reviews	48
	Titles database	**189**
	Titles all databases	**1373**
	Included title	**523**
	Included abstract	**182**
	Included article	**48**
	"Snow-ball articles"	**2**
	Total articles	**50**

11.1.2 Data extraction tables

Reference	Ref-id	
	Author	
	Year	
	Study – ICD exposure	
	Study – ICD prognosis	
	Study– indiv. risk factors	
	Other, commentary	
Study design	□ Cohort- prospective	
	□ Cohort- retrospective	
	□ case control	
	□ cross sectional	
	other, specify	
Population (specify for exposed and controls) (participation rate)	Country	
	□ General population	
	□ Industry workers	
	□ Convenience Sample	
	Other, specify	
Men, exposed/ controls	n=	
	Average age	
	Range Age	
	Remarks	
Woman, exposed / controls	n=	
	Average age	
	Range Age	
	Remarks	
Total, exposed/ controls	n=	
	Average age	
	Range Age	
	Remarks	
Quantitative exposure assessment	Measured Yes/no	
	Conc range	
	Total/average conc	
	□ individual masurements	

	□ group measurements	
	□ area measurement	
	Other specify	
Semi-Quantitative exposure assessment	□ expert judgement	
	□ JEM	
qualitative exposure assessment	□ self-report	
	□ home	
	□ industry	
	□ occupation	
Remarks exposure assessment		
Type of Exposure		
More exposures		
Type of occupation		
Diagnosis	Diagnosis /Outcome	
	□ clinical	
	□ self-report	
	□ register based	
	□ industry	
	□ occupation	
	Diagnostic criteria used	
	Remarks	
Men	OR (CI)	
	RR (CI)	
Woman	OR (CI)	
	RR (CI)	
Total	OR (CI)	
	RR (CI)	
Dose-response performed?	yes/no	
	Range exposure /conc. /time/times	
	RR (CI) for exp. /conc/time etc	
Covariates	□ allergy /patch test rele-	

adjusted for	vant allergens	
	□ atopy	
	□ gender	
	□ age	
	□ private exposures	
	others, specify	
the exposure adequately described?	□ yes	
	□ yes, partly	
	□ no	
	□ no mention	
	□ n/a (ikke relevant)	
	□ do not know	
Is the outcome adequately described?	□ yes	
	□ yes, partly	
	□ no	
	□ no mention	
	□ n/a (ikke relevant)	
	□ do not know	
Was the measurement of the outcome sound?	□ yes	
	□ yes, partly	
	□ no	
	□ no mention	
	□ n/a (ikke relevant)	
	□ do not know	
Adequately corrected for confounders?	□ yes	
	□ no	
	□ n/a (ikke relevant)	
	□ do not know	
	If no data probably confounded by:	
Data probably biased?	□ no	
	□ yes, partly	
	□ yes	
	□ misclassification of exposure	
	□ misclassification	

	of outcome	
	□selection of study population	
	□other, specify:	
Are the statistical analyses appropriate?	□ yes	
	□ yes, partly	
	□ no	
	□do not know	
Are the results probably due to chance?	□ yes	
	□ yes, partly (CI contains 1 or p-value >0,05)	
	□ no	
Grading of the study	1 (best)	
	2	
	3	
	4	
	5 (not suitable)	

Grading	Score 1	Score 0	
Study	Cohort study or case control study with population or hospital controls	Case control study with convenience controls. Cross- sectional studies	
Number of participants	>=75 cases	<75 cases	
Response rate	> 60%	≤ 60%	
source of exposure information	non-self-reports	self- reports	
exposure measure:	quantitative or semi-quantitative	qualitative	
source of diagnosis	Hospital/clinical	vs. surveillance schemes, self-reported or not well-defined sources	
diagnosis	well defined diagnostic criteria	other criteria	
possible confounding	accounted for atopy, age and sex in adjusted analyses or by matching	no account atopy, age and sex.	

11.1.3 Evidence criteria causal association

Degree of evidence of a causal association between an exposure to a specific risk factor and a specific outcome. Criteria of the Scientific Committee of the Danish Society of Occupational and Environmental Medicine

Description of categories:

Strong evidence of a causal association (+++):

A causal relationship is very likely. A positive relationship between exposure to the risk factor and the outcome has been observed in several epidemiological studies. It can be ruled out with reasonable confidence that this relationship is explained by chance, bias or confounding.

Moderate evidence of a causal association (++):

A causal relationship is likely. A positive relationship between exposure to the risk factor and the outcome has been observed in several epidemiological studies. It cannot be ruled out with reasonable confidence that this relationship can be explained by chance, bias or confounding, although this is not a very likely explanation.

Limited evidence of a causal association (+):

A causal relationship is possible. A positive relationship between exposure to the risk factor and the outcome has been observed in several epidemiological studies. It is not unlikely that this relationship can be explained by chance, bias or confounding.

Insufficient evidence of a causal association (0):

The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of a causal association.

Evidence suggesting lack of a causal association (-):

Several studies of sufficient quality, consistency and statistical power indicate that the specific risk factor is not causally related to the specific outcome.

Comments:

The classification does not include a category for which a causal relation is considered as established beyond any doubt.

The key criterion is the epidemiological evidence.

The likelihood that chance, bias and confounding may explain observed associations are criteria that encompass criteria such as consistency, number of 'high quality' studies, types of design etc.

Biological plausibility and contributory information may add to the evidence of a causal association.

11.1.4 Table 11 Studies on individual risk factors

Table 11 present characteristics from 10 papers from 10 studies involving individual risk factors for ICD and skin changes from 2010 and later

Table 11	Studies on individual risk factors (2010 and later)						
Author Year Country (ref.)	**Study Design**	**Study population Exposed/ controls (participation rate); Age mean(SE) or median, range**	**Individual risk factor, definitions and measurements**	**Exposure, exposure assessments, type of occupations**	**Outcome – Diagnostic criteria**	**Covariates accounted for**	**Result** **Total OR/RR (95% CI)**
Mortz 2014(47) Also, table 8	Prospective cohort study of young adults from general population 15 year after baseline study in 8'th grade. Questionnaire and clinical examinations at baseline and f-up.	Questionnaire 899 (60% of baseline, 75% of contacted at f-up). Clinical exam. 469 (31% of baseline, 39% of contacted at f-up) ♀ 56% 28-30 years	AD Previous HE at age 13-14 Caring for children<4 yr, >2 hrs./day Smoking Sex	Self-rep. exp. wet work, other work exp. hand washing, daily use of occlusive gloves	HE Used NOSQ 2002 standardized questionnaire, with criteria self-rep. HE: history of eczema on hands, once for >2 weeks or relapsing or persistent. For subgroup Clinical HE: inflammation with itching erythema, papules and/or vesicles and scaling at hand for ≥ 2 days. Patch test incl.	Wet work.	Self-rep. current HE adj. ass, OR: AD: 1.9 (1.2-3.0), Previous HE (age 13-14): **4.2 (2.3-7.5);** Caring for children <4 year >2 hrs./day: **1.7 (1.1-2.8),** Smoking NS 1.4 (0.9-2.1), male sex NS 0.66 (0.4-1.1)
Lee 2013 (94) Korea Also, table 8	CS study in hospital of nursing staff using questionnaire and patch testing on subpopulation of workers reporting HE	525 (75%) ♀ 97.1 % 38.8; 21-58 years	Self-rep: history of AD.	Self-rep: daily hand washing freq., daily glove wearing time, daily use of hand moisturizer, use of alcohol based skin rubs, duration of employment, depart-	HE: Self-rep. HE last 12 months, symptom-based HE (pos. reply 1 of 6 symptoms). ACD: relevant pos. patch tests in 43 of subgroup of 70 (43%) of workers with	Hand washing, glove wearing, use of moisturizer, sex	Adj. analyses HE ass. risk factor, OR's: Atopic dermatitis: 2.33 (1.06-5.15) Age (continuous variable): 0.95 (0.90-1.00) p=0.04 No ass. hours of housework (data n.r)

Table 11	Studies on individual risk factors (2010 and later)						
Author Year Country (ref.)	**Study Design**	**Study population Exposed/ controls (participation rate); Age mean(SE) or median, range**	**Individual risk factor, definitions and measurements**	**Exposure, exposure assessments, type of occupations**	**Outcome – Diagnostic criteria**	**Covariates accounted for**	**Result** **Total OR/RR (95% CI)**
				ment	HE.		
Visser 2013 (40) The Nederlands (same study as (95)) Also, table 8	1-3 years prospective cohort study of apprentice nurses from 15 vocational schools. Entry questionnaire, diary cards during f-up recording exposure and skin symptoms. Genotyping.	533 (73%), f-up 1,2 or 3 years, 445 without previous HE. 626 DNA samples, 596 genotyped for four FLG loss mutations. Age median (25-75%): 19.5 (18.3-20.9) years ♀ 90 %	History of AD (defined according to the UK working party criteria (ref 2110) modified to onset below age 5.) FLG loss mutations measured DNA samples. Self-rep. freq. handwashing at home.	Wet work activities: hand washing, use of alcohol rubs, wearing gloves, other contact with water, soap and disinfectants reported/measured freq. and duration on diary cards every 2-4 weeks.	HE: self-rep. fissures combined with redness, itch or scaling, vesicles or papules for >3 days recorded on diary cards every 2-4 weeks. Mild HE: combination self-report. redness, scaling, fissures, vesicles or papules of any duration.	Handwashing freq. at work, side job wet work	Adj. analysis HE & HE during traineeship with no previous HE or wet work exp. OR: FLG mutations and AD, ref. FLG-/AD-: FLG+/AD-: 0.7 (0.3-1.7) & 0.5 (0.1-1.9) FLG-/AD+: **2.2 (1.4-3.4)** & 1.4 (0.7-2.9) FLG+/AD+:**3.6 (1.7-7.5)** & **3.7 (1.0-13.5)** Weighed OR HE, AD: 2.5. Hand washing at home >10 times/day: 1.0 (0.7-1.5) & 1.2 (0.6-2.1)
Callahan 2013 (85) USA Also, table 7	6-month prospective study of volunteer HCW, washing hands ≥8 times/day. Baseline questionnaire and patch test for skin irritants. Clinical exam at 1 month interval.	113 volunteers, % of pop. n.r. 102 (90%), 12 with baseline ICD of hands incl. analysis. ♂ 64% Age 32 (9.6)	Atopy def. as history of childhood flexural dermatitis. Baseline patch test for skin irritancy (24h) to SLS, NaOH and BKC. Responders when irritant reaction at 2.5% SLS, 1% NaOH, 0.5% BKC.	Self-rep. daily handwashing. HCW.	ICD hands diag. clinical. ICD classified active dermatitis/eczema & minor dermatitis (erythema, slight chapping and scaling).	Age, sex, ethnicity, exp. handwashing, gloves, sanitizers. Season, Indoor humidity.	Adj. PR ICD hands Atopy (yes vs. no) 0.86 (0.49-1.49) SLS responder (yes vs. no): **1.87 (1.06-3.31)** No ass. response NaOH or BKC Adj. IRR ICD hands: Atopy (yes vs. no): 1.08 (0.61-1.93) SLS responder (yes vs. no) 1.78 (0.92-3.45) No ass. response NaOH or BKC.
Landeck 2013 (134) The Nederlands	CC study on effect of Interleukin-1-α gene polymorphism on ICD. Cases and controls as (41)	As. (38)	Interleukin-1-α polymorphisms of IL1A-889 assessed DNA samples.	As (38)	As (38)	No ass. genotype and flexural eczema or wet work exp.	Trend neg. ass. OICD and ILA-889 T vs. C allele, OR 0.81 (0.65-1.00) No S ass. genotype when stratified atopic ICD and non-atopic ICD

Table 11	Studies on individual risk factors (2010 and later)						
Author Year Country (ref.)	**Study Design**	**Study population Exposed/ controls (participation rate); Age mean(SE) or median, range**	**Individual risk factor, definitions and measurements**	**Exposure, exposure assessments, type of occupations**	**Outcome – Diagnostic criteria**	**Covariates accounted for**	**Result** **Total OR/RR (95% CI)**
Landeck 2012 (38) Germany	CC study on effect of TNF-α polymorphism on ICD. Cases and controls as (41)	478 (93% of 712, 178 excl.) / 393 (95% of 500, 84 excl.) ♀ %: 60 / 61 Median 43/19, 18-67/16-56 years	TNF-α polymorphisms of TNFA-238 and TNFA-308 assessed DNA samples.	Self-rep. wet work, classified (≤2, 2-4, >4 hrs./ day). Various occupations, as (41)	ICD +/- atopy. Atopy: clinical based ongoing/past flexural eczema and/or ≥10 points Erlangen atopy score.	No ass. genotype and flexural eczema or wet work exp.	OR ICD TNFA-308 A vs. G allele **1.33 (1.02-1.74)** TNFA-238 A vs. G allele **0.57 (0.34-0.97)** No S ass. genotype when stratified atopic ICD and non-atopic ICD.
Visser 2012 (41) Germany	CC study with FLG genotyping. Cases: OICD patients from occupational clinic. Controls: vocational trainees in similar high-risk occupations for HE answering questionnaire.	634 (100%) / 393 (95% of 500, 84 excl.) ♀ %: 62 / 62 Median (25-75%) 43 (31-51) / 19 (18-22) years	FLG loss of function mutations in DNA samples. History of AD: Current or past flexural eczema in patients, self-rep flexural eczema controls. AD controls validated dermatological exam. subset of 245 controls.	Various occupations, 72%/69% of cases/controls hairdressing, HCW or Metalwork/mechanics	OICD. Cases diagn. clinical by dermatologist. Criteria cases based history, presentation, exp. to irritants, no clinical relevant type-IV sensitization at patch test.	Age (separate adj. analysis) Sex	PP cases / controls % *AD: 18.7 / 41.1, FLG mutations 15.6 /8.6.* Adj. OR ICD AD vs. non-AD: **2.89 (2.08-4.03**) FLG + vs - mutations: **1.61 (1.01-2.58)**
Kütting 2011 (135) Germany	Prospective cohort study of metalworkers, mainly shift-workers from 19 small, medium-sized factories.	Baseline 1,020 of 1,355 1 year, f-up 1,020 (75%) 406 smokers, 614 non-smokers. Baseline: ♂ 96.7 %, 41, 17-64 year ♀ 3.3%, 37, 17-59 year	Self-rep. smoking in questionnaire at baseline.	Metalworkers.	ICD Clinical examinations using HEROS quantitative skin score. No patch tests. Self-rep. dyshidrotic vesicles	No adjusted analyses.	Smokers vs. non-smokers at 1 year- f-up: Dyshidrotic vesicles last ½ year: 9.5% vs. 5.3%, p=0.027 Current topical steroids: 2.9% vs. 1.0%, p=0.038 Mean HEROS scores Total score: 16.9 vs. 16.0 NS Erythema: 6.2 vs. 5.5, p<0.01 Vesicles: 0.14 vs. 0.03, p=0.02 No difference erosions, scabs, fissures or excoriations.
Lan 2011 (93) Taiwan Also, table 8	CS study of 1132 Nurses from university hospital. Study 1.	1132 (93%) ♀: 99 %	Atopic eczema – diagnosed according to Hanifin and Rajka criteria during the past year. Self-rep. housework hrs. pr. week	Handwashing, hand rub, gloves. HCW.	HE based on diagnostic algorithm of symptoms validated in different study.	Year work experience, work section	Adj. OR HE: Atopic eczema**: 3.77 (2.40-5.90)** Housework >10 hrs./week: 1.46 (0.94-2.25)

Table 11	Studies on individual risk factors (2010 and later)						
Author Year Country (ref.)	**Study Design**	**Study population Exposed/ controls (participation rate); Age mean(SE) or median, range**	**Individual risk factor, definitions and measurements**	**Exposure, exposure assessments, type of occupations**	**Outcome – Diagnostic criteria**	**Covariates accounted for**	**Result** **Total OR/RR (95% CI)**
Apfelbacher 2010 (74) Germany Also, table 7	Nested CC studies on prevalent cases of HE and subgroup of ICD from 13 years. f-up studies in the car manufacturing industry. Controls random samples of non-cases from same population.	Cases/controls ICD 57/120, ♂ 86.0 % / 84.2%. Age 28.9/29.3 years	Atopy (ASD) assessed by standardized validated atopy score (Erlangen Score, Diepgen) >10 points. Flexural eczema	Qualitative exp. wet work, dry skin soiling, W-MWF, O-MWF, solvents. Metalworkers, office workers, other blue-collar workers.	ICD: HE recorded as irritant by dermatologist.	Age, sex, occupational and domestic exposure	Cases vs. controls: PP* flexural eczema, 3,5%, 2,5%., ASD 26.3% vs. 10.9%. OR* 1.42 NS, **2.91** (1.17-7.24) Adj. analysis OR ASD **1.84** (1.20-2.80)

Diagnoses: ACD: Allergic contact dermatitis; AD: Atopic dermatitis; HE: Hand eczema; ICD: Irritant contact dermatitis; OICD: Irritant occupational contact dermatitis;
Exposures and confounders: exp: exposure; MWF: Metal working fluids; W-MWF: water-based MWF=soluble MWF; O-MWF: oil-based MWF=neat/insoluble MWF
HCW: Healthcare workers; FLG
Study characteristics: adj: adjusted; ass: association; CC: case control; CS: cross sectional; f-up: follow-up; exam: examination; freq: frequent; hrs.: hours; incl: included;; neg: negative; n.r: not reported; NS: non-significant; OR: odds ratio; PP: Prevalence proportion; PR: Prevalence ratio; S: significant; self-rep: self-reported; vs.: versus
* Calculated from data I article