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Protocol for a systematic review on skin and systemic toxicity of important hazardous substances in hair cosmetics and hand eczema in hairdressers

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Protocol for a systematic review on skin and systemic toxicity of important hazardous substances in hair cosmetics and hand eczema in hairdressers

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Abstract

Introduction

Hairdressers constitute a major subgroup in the service sector. They are exposed to various substances hazardous for skin, airways, or systemically. Accordingly, skin and other occupational diseases are common. The present systematic review will compile and appraise evidence regarding skin, systemic and airways toxicity of an indicative set of specific, important product ingredients. Additionally, evidence concerning hand eczema morbidity among hairdressers will be reviewed.

Methods and analysis

Systematic searches will be performed in 2 electronic literature databases (Medline, Web of Science–Core Collection), the Cochrane register and two collections of toxicological dossiers (SCCS/EU and German MAK Commission). Additional literature sources will be retrieved using hand search of reference lists of included studies and snowballing methods. We will include studies with all types of quantitative study designs, including results from *in vitro* and *in vivo* experiments, chemical analysis, epidemiological findings, and clinical results. We will assess the risk of bias within studies with an abbreviated version of the MMAT appraisal. As we expect large heterogeneity in methods and outcomes, we will conduct a narrative synthesis of results instead of a meta-analysis, except where quantitative pooling is feasible.

Ethics and dissemination

Ethical approval and patient consent are not required as this is a systematic review based on published studies. The results of this study will be published in international peer-reviewed journals.

Prospero registration number

to follow (registration has been applied for on 19 Feb. 2021).

Keywords:

systematic review, hairdressers, occupational diseases, workers' health, skin diseases, airways disorders, systemic toxicity

Article summary (strengths and limitations of this study)

- Exhaustive search for relevant studies in the most relevant databases and through additional literature sources.
- This review is not limited to specific study designs or participant groups.
- Due to expectedly very heterogeneous methods and outcomes, we will have mostly to undertake narrative synthesis instead of meta-analysis.

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[3]

Introduction

The hairdressing sector in the EU is dominated by small- and micro-businesses with some 400,000 salons employing over 1.5 million workers, which amounts to approx. 10% of the total service sector in Europe. In order to ensure good health conditions within the workforce and subsequently avoid a loss of working hours, health and safety are crucial issues. In everyday work, hairdressers are in contact with many hazardous and toxic agents, which entails different occupational health risks such as skin damage, respiratory problems, reproductive disorders, various forms of cancer, etc. Additionally, evidence concerning the morbidity of hand eczema among hairdressers will be reviewed.

Research has shown that up to 70% of hairdressers suffer from work-related skin damage, mostly hand dermatitis, at some point during their career. The most important risk factors for developing occupational skin diseases (OSD) are wet work and occupational contact to irritants, as for example detergents or hairdressing chemicals, and allergens. In Europe, OSD represent up to 35% of all reported occupational diseases, and the often chronic course causes extensive suffering for the affected workers. The economic burden of OSD in the EU exceeds € 5 billion p.a., spent on treatment, compensation, and loss of productivity. The chronic course of OSD, mainly irritant and allergic contact dermatitis of the hands, may result in detrimental socio-economic consequences, e.g. job loss and long-term unemployment.

Other occupational health problems of hairdressers are respiratory disorders related to inhalation exposure to hazardous chemicals from the used products, e.g. hair sprays. Aerosols are widely encountered in hairdressing and may reach the lungs, depending on particle size. Bleaches and hair sprays are emphasized by hairdressers as the most irritative substances for airways at their workplace.[1] Ammonia is an irritating chemical present in the air of hairdressing salons during bleaching or perm procedures, often in concentrations exceeding occupational exposure limits, as is formaldehyde during hair straightening procedures.[2–4] According to epidemiological evidence, hairdressers and hairdressing apprentices are prone to irritation of the upper airways, reporting symptoms of watery nose, nasal congestion, and cough in higher proportions than control subjects unexposed to chemical irritants.[5, 6]

EU cosmetics legislation restricts the use of carcinogenic, mutagenic, or toxic for reproduction (CMR) substances. Exceptions to this general rule are possible subject to the conditions laid down in Article 15 of the Cosmetics Regulation EU 1223/2009. For example, a substance classified in category 2 may be used in cosmetic products where the substance has been evaluated by the Scientific Committee on Consumer Safety (SCCS) and found safe for use in cosmetic products. However, professionals are qualitatively and quantitatively much more exposed to such substances than a typical consumer or client. As one example, hairdressers apply colour about 6 times a day with their hands – which might already be previously damaged by occupational skin strains – being exposed, sufficiently protected or not by gloves, as opposed to consumers who apply on average once every 4 weeks a permanent colouring, exposing both hands and scalp. The specific professional exposure is normally not assessed in SCCS opinions, even though special aspects may be mentioned and referred to the Risk Assessment Committee. Thus, safety concerns related to occupational exposure remain. Indeed, in a monograph published in 2010, the International Agency for

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Research on Cancer (IARC) confirmed that the occupational exposure of hairdressers should be considered as probably carcinogenic (IARC group 2A) [7]. A new strategy for chemicals are currently being developed in EU (https://ec.europa.eu/environment/strategy/chemicals-strategy_en) making a compilation of evidence especially relevant. Hence, in the context of the project "Promoting the autonomous implementation of the European framework agreement on occupational health and safety in the hairdressing sector," a series of systematic reviews will be performed, the methods of which are described in the present publication.

Methods and analysis

Patient and public involvement

Patients and/or the public were not involved in the development of this research project; however, stakeholders from the occupational insurance and employers and employees' associations, respectively, have provided input regarding the scope of substances to assess.

Design

This study will be a systematic review with primarily narrative data synthesis and will be based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) checklist.[8] In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

Eligibility criteria

Eligibility criteria for studies to be included in the systematic review are reported following the PECOS scheme adapted from (University of York 2009, [9]) in table 1.

The scope of the systematic review, while focusing on workers in the hairdressing trade, is not limited to this particular subgroup, that is, clinical studies illustrating exposure to, and morbidity from, chemicals in hair cosmetics in other groups will be considered, too. The focus of this systematic review is on a quantitative assessment of the morbidity in terms of skin toxicity (mostly contact allergy) and systemic toxicity (e.g. CMR; see table 1) in humans as well as on *in vivo* and *in vitro* results regarding these respective toxicological endpoints. Furthermore, the overall morbidity of hand eczema among hairdressers will be quantified. We will include all types of studies with quantitative empirical data (see Table 1). Observational studies are likely to be the most important source of information for this review, supplemented by basic research evidence derived from *in vivo* and *in vitro* methods.

Target substances

Following deliberations within the project consortium and following the proposed potentially problematic types of products considered in this project (Table 2), a DELPHI survey was held shortlisting altogether 33 substances. Feed-back was provided by 48 of 121 experts and stakeholders invited (response: 39.7 %). After initial candidates had been removed as they were regarded as irrelevant for the purpose, and additional entries had been added, the remaining above-threshold candidates were eventually consented by the research consortium and finally included in the list of substances to be considered, shown in Table 2.

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Searches

We will conduct systematic searches using the following electronic databases: Pubmed/Medline and Web of Science–Core Collection (WoS). Additionally, the Cochrane registry, and the archive of scientific opinions of the Scientific Committee on Consumer Safety (SCCS) of the European Commission and its predecessors will be searched for studies, reviews and opinions (the latter normally concluding on data submitted by industry concerning the safety of a cosmetic ingredient; https://ec.europa.eu/health/scientific_committees/consumer_safety_en, last accessed 10 Feb. 2021). As far as available, dossiers in English language of the German "MAK Commission" on the substances available will be identified and used in the synopsis and discussion of results (https://onlinelibrary.wiley.com/doi/book/10.1002/3527600418, last accessed 10 Feb. 2021). All searches will be performed at the very start of the project. Furthermore, we will hand search the bibliographies of all studies identified through the electronic database search and meeting the inclusion criteria. We will also perform forward-snowballing by using the six most important references identified, and check all references citing any of these publications. This citation analysis will be performed based on the WoS database.

Concerning those substances where an abundance of data exists on any one of the toxicological endpoints which has been summarised adequately in the past, only literature published since then will be searched for. We will use English search terms only. Generally, title, abstract and key words will be the items to be searched.

The searches are composed of the following modules: (i) substance identifiers ("SUB"), (ii) skin toxicity endpoints ("SKIN"), and (iii) systemic/respiratory toxicity endpoints ("SYS") which are defined below. Moreover, the searches will be split into the following topics, using the same set of substance identifiers as common denominator:

- "SUB" AND "SKIN": this, and the following, combination will be used to identify all studies contributing evidence to the endpoints, whether or not related to exposure as hairdresser
- "SUB" AND "SYS": as above

SUB

Substance identifiers include all relevant MeSH terms and important synonyms. The latter include the preferred chemical (IUPAC) name as well as the INCI (International Nomenclature of Cosmetic Ingredients) term, along with CAS no. and synonyms – but excluding trademarks – identified in the CAS database (SciFinder^{TM}). The substance identifiers are shown in the online supplemental **appendix A**. In order to increase the sensitivity of the search, at some expense on its specificity, product (group) descriptors are additionally employed in the search for relevant substances, joined by an OR operator, and "hairdress*" as reference to "hairdressing products," but also to the job title, as shown below. Pilot searches in Medline of the suggested terms combined with "contact AND dermatitis" (CD) and "contact AND allergy" (CA), respectively, yielded meaningful results; the number of references is indicated in parentheses after each search string:

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- hairdress* (n=305 along with CD, n=228 with CA, resp.)
- hair dyeing (n=48 along with CD, n=44 with CA, resp.)
- hair coloring (n=193 along with CD, n=153 with CA, resp.)
- permanent wave (n=30 along with CD, n=18 with CA, resp.)
- acid perm (n=1 along with CD, n=1 with CA, resp.)
- persulfate* (n=57 along with CD, n=48 with CA, resp.)
- persulphate* (n=15 along with CD, n=10 with CA, resp.)

SKIN

Endpoint / disease identifiers include the relevant MeSH terms and common medical language synonyms listed below:

Allergens[MeSH] OR Haptens[MeSH] OR agents, contact sensitizing[MeSH] OR allergic OR Dermatitis, Allergic Contact[MeSH] OR Dermatitis, Contact[MeSH] OR contact allergy OR Skin Tests[MeSH] OR Local Lymph Node Assay[MeSH] OR guinea pig maximization test OR Patch Tests[MeSH] OR Skin Irritancy Tests[MeSH] OR contact dermatitis OR contact urticaria OR contact sensitization OR Occupational Diseases[MeSH] OR work related

SYS

Endpoint / disease identifiers include the relevant MeSH terms and common medical language synonyms listed below:

Allergens[MeSH] OR Irritants[MeSH] OR allergic OR irritative OR Respiration Disorders[MeSH] OR respiratory OR Inhalation[MeSH] OR Rhinitis[MeSH] OR Asthma OR Neoplasms[MeSH] OR cancer OR Carcinogens[MeSH] OR Biomarkers, Tumor[MeSH] OR Carcinogenicity Tests[MeSH] OR Mutagens[MeSH] OR Mutagenicity Tests[MeSH] OR genotoxicity OR Reproductive Health[MeSH] OR reproductive toxicity OR reprotoxic OR Pregnancy Outcomes[MeSH] OR Pregnancy Complications[MeSH] OR Pregnancy[MeSH] OR Infertility[MeSH] OR Congenital Abnormalities[MeSH] OR birth defect OR congenital malformations OR Abortion, Spontaneous[MeSH] OR Developmental Disabilities[MeSH] OR developmental toxicity OR Menstruation Disturbances[MeSH] OR Spermatogenesis[MeSH] OR Fertility[MESH] OR Fecundability OR Time to pregnancy OR low birth weight OR Endocrine Disruptors[MeSH] OR Endocrine System Diseases[MeSH] OR Toxicity Tests[MeSH] OR Toxicity Tests, Acute[MeSH] OR Toxicity Tests, Subacute[MeSH] OR Toxicity Tests, Chronic[MeSH] OR Toxicity Tests, Subchronic OR dermal absorption OR Occupational Diseases[MeSH] OR work related OR hairdresser* OR hairdressing

Hand eczema

To identify studies concerning the morbidity of hand eczema among hairdressers, the following search, combining free text and MeSH terms will be used:

((Hairdresser* OR Hairdressing apprentice*)
AND
(“Dermatitis”[MeSH] OR Dermatitis OR “hand eczema” OR “contact allergy” OR “allergic contact dermatitis” OR “irritant contact dermatitis” OR “occupational dermatitis” OR “skin”[MeSH])

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[7]

AND
("Morbidity"[MeSH] OR "Risk"[MeSH] OR prevalence OR incidence OR Hazard OR consequences OR severity))

Further restraints

Only accepted publications newer than 1999 (i.e., 2000 and following) will be considered.

Data management

For one search query (e.g. skin toxicity), the search results will be exported from Medline and WoS in a suitable format and imported into Zotero libraries, documenting the number of references contributed by each ex-/import set. In the Zotero library, bibliographical duplicates will be identified and the entry including less information (e.g., no abstract) be discarded. Each entry will be identified by a unique, human readable ID generated by using the BetterBibtex Plug-in, with manual editing where necessary. The remaining unified library will be exported in RIS format and imported into a new Rayyan project (Rayyan QCRI, https://rayyan.qcri.org/welcome, last accessed 21 Feb. 2021) for shared screening by two reviewers for eligibility based on title, key words and abstract. In case of discordant results, the entry will be reviewed by a third experienced reviewer and a final decision be made. Reasons for non-inclusion will be documented, and summarised at the end for use in the PRISMA-P flowchart.

Study selection

The final set of references deemed eligible for full text screening by above-mentioned two reviewers will be exported from Rayyan in Bibtex format for import into the Zotero cloud-based reference database, after the intial set of references has been archived. Zotero offers freely definable "tags" for entries. These will be used to identify which of the selected substance(s) is/are treated in the article (see shorthands for substances in Table 2); these tags will be added when scrutinising and extracting the full text articles, again, independently by two reviewers, with a third senior reviewer consensualising divergent results between the two initial reviewers. All decisions and reasons leading to the exclusion of studies at this stage will be documented, providing information on the individual assessments by both intial reviewers and the final decision. At the end of this process, a set of full text articles to be included in the systematic review will be identified.

Data extraction

Two reviewers will independently extract the data from studies meeting the inclusion criteria using standardised, pre-piloted publication record forms (PRFs). There will be different PRFs, owing to the different methodology and outcomes generated, according to study type. Thereby, one form each will be used for (i) clinical patch test studies, (ii) other observational studies addressing respiratory and systemic diseases, (iii) experimental (*in vivo* and *in vitro*) studies, and (iv) morbidity of hand eczema. A third senior reviewer will review the extracted data and make final decisions in contradictory cases. The following basic data will be extracted for observational studies: Publication ID, year of study execution, country of origin, study design, methods, study setting and population involved, information on basic characteristics of participants (eg, age, gender, ethnicity), number of

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participants, number of positive outcome(s), and funding source. For experimental studies, publication ID, year of study execution, country of origin, study design, methods, study setting, test system/animals, number of observational units, outcomes (mean and spread), and funding source will be documented. Outcomes will be extracted in subcategories as defined in Table 3 to enable meaningful data synthesis and analysis. Finalised PRFs will be preserved and published as supplemental material to the systematic review.

If necessary, outcome information will be approximated from figures in the reports. If more than one publication reports on the same study we will combine information from the publications if they report on different outcomes and use the more comprehensive one(s) if the shorter one(s) do(es) not add any additional information. If any contradictions with regards to content appear between such multiple publications, we will extract the information given in the more recent publication. We will contact study authors by email if important methodological details are missing.

Risk of bias within included studies and quality of evidence assessment

Suitable criteria for assessing risk of bias and quality of evidence will be applied. Two reviewers will independently appraise studies meeting the inclusion criteria after full text scrutiny without being blinded to the studies. The published MMAT appraisal will be used on the study level in case of homogeneous methodology, and on the outcome level in case of multiple methodologies used in one study.[10] Moreover, a global rating as high, moderate, low, and very low of study quality will be assigned to all studies by each of the reviewers, following criteria of the GRADE approach [11].

Data synthesis and analysis

There will be substantial heterogeneity both in methodologies (even in the sub-categories of “experimental” and “clinical” research) and in outcomes. Instead of a meta-analysis, we will primarily conduct a narrative synthesis following guidance from the Centre for Reviews and Dissemination.[9] Summary tables will present the main characteristics of the included studies, their finding as well as their quality rating. Notwithstanding, if for a subset of eligible studies a quantitative summary appears feasible, in view of sufficiently uniform methodology and outcome definition, graphical summaries as Forest plots with an assessment of heterogeneity (I^2) will be presented. In such cases, the strenght of cumulative evidence will be assessed using the GRADE criteria.[11] Apart from a results presentation evidently stratified for the substances concerned, subgroup analyses or meta regression approaches are not foreseen.

Ethics and dissemination

Ethical approval and patient consent are not required as this is a systematic review based on published studies. This systematic review has been registered in PROSPERO (XXXXXXXXXXXXX, registration pending). The results of this review will be published in international peer-reviewed journals.

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Protocol amendments

This is the initial version of the study protocol. Amendments to the protocol will be filed with PROSPERO and listed in the results publication(s), which will otherwise refer to the present publication.

Author Contributions (CRedIT)

Wolfgang Uter: Conceptualization, Methodology, Resources, Writing - Original Draft; **Jeanne D. Johansen:** Conceptualization, Methodology, Writing - Review & Editing; **Martin S. Havmose:** Conceptualization, Writing - Review & Editing; **Sanja Kezic:** Conceptualization, Methodology, Writing - Review & Editing; **Henk F. van der Molen:** Methodology, Writing - Review & Editing; **Jelena Macan:** Conceptualization, Methodology, Writing - Review & Editing; **Rajka Turk:** Conceptualization, Methodology, Writing - Review; **Željka Babić:** Conceptualization, Methodology, Writing – Review; **Cara Symanzik:** Conceptualization, Methodology, Writing - Review; **Swen M. John:** Conceptualization, Methodology, Writing - Review & Editing, Project administration, Funding acquisition, Guarantor of the review. All authors have read and approved the final submitted version of the manuscript.

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Conflict of interests

W.U. has received a honorarium for a lecture on contact allergy from mixed dermatopharmaceutical sponsors (GEIDAC, Toledo, Sept. 2018) and travel reimbursement for participation in study meetings of the IDEA project (IFRA). W.U. is external expert for the SCCS. Other authors: None to declare. Provenance and peer review: Not commissioned; externally peer reviewed.

Data statement

Not applicable (no original data).

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Table 1: Eligibility criteria following the PECOS scheme, adapted from (University of York 2009)

Criterion	Inclusion	Exclusion
Participants	Hairdressers, patients, cosmetic products	None
Exposure	Exposure to (an) eligible chemical(s)	N/A
Comparator	Clients, consumers, normal population (no, or less, exposure)	N/A
Outcome	Skin toxicity event (contact allergy, irritancy)	N/A
	Systemic toxicity (CMR, ED, respiratory)	N/A
Study design	Experimental studies, e.g.	Qualitative studies
	Chemical analyses	
	in vivo Toxicological studies	
	in vitro Toxicological studies	
	Observational studies, e.g.	
	Case–control studies	
	Prospective and retrospective cohort studies	
	(Repeated) cross-sectional studies	
	Case reports, clinical series	

CMR, carcinogenicity/mutagenicity/reproductive toxicity; ED, endocrine disruption; N/A, not applicable.

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[11]

Table 2: List of most relevant product groups in hairdressing with substances finally included into the systematic review

	Product category	Substance(s)
1	Oxidative hair dyes/colorants	*p*-Phenylenediamine (PPD; CAS no. 106-50-3) and its salts (CAS no. 624-18-0, 16245-77-5), toluene-2,5-diamine (PTD; CAS no. 95-70-5) and its sulfate (CAS no. 615-50-9), 2-Methoxymethyl-PPD (mePPD; CAS no. 337906-36-2)
2	Bleaches	Persulfate salts: ammonium, APS, CAS no. 7727-54-0; potassium, PPS, CAS no. 7727-21-1; sodium, SPS, CAS no. 7775-27-1
3	Perms and relaxing substances	Salts and esters of thioglycolic acid: glyceryl thioglycolate (GMTG; CAS no. 30618-84-9), ammonium thioglycolate (ATG; CAS no. 5421-46-5)
4	Cosmetic glues	2-Hydroxyethyl methacrylate (HEMA; CAS no. 212-782-2), ethyl cyanoacrylate (ECY; CAS no. 7085-85-0)

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Table 3: Subcategories of outcomes

- Skin toxicity
  - Skin sensitisation / contact allergy in humans (e.g., numbers tested, numbers positive, test methods)
  - Skin irritation in humans (e.g., exposure conditions leading to irritation)
  - Sensitisation *in vivo* or *in vitro* (e.g., guideline vs. non-guideline method, main read-out such as EC3-value for LLNA)
  - Irritancy *in vivo* or *in vitro* (e.g., guideline vs. non-guideline method, main read-out)
- Systemic toxicity
  - Carcinogenicity/cancer risk in humans (e.g., epidemiological studies on occupational vs. consumer exposure)
  - Carcinogenicity *in vivo* or *in vitro* (e.g., mechanistic studies, tumor promoting activity and frequency of tumor incidence)
  - Mutagenicity *in vivo* or *in vitro* (e.g., genotoxicity tests, main read-out)
  - Reproductive and developmental toxicity in humans (e.g., menstrual disorders, sperm production, pregnancy and birth outcomes)
  - Reproductive and developmental effects in vivo (e.g., male and female reproductive effects, developmental and post-natal toxicity)
  - Endocrine disruption *in vivo* or *in vitro* (e.g. test methods, adverse effects on endocrine relevant endpoints, endocrine/androgen/thyroid/steroidogenesis)
- Respiratory toxicity
  - Airways sensitization and irritation in humans (e.g. inhalatory exposure, inhalatory allergens, respiratory irritants, asthma, rhinitis, occupational diseases)
- Hand eczema
  - Hairdresser/hairdressing apprentice
  - Gender
  - Morbidity (prevalence, incidence)
  - Debut (onset)
  - Severity/frequency of eruptions
  - Concomitant atopic dermatitis
  - Diagnosis (self-reported vs. physician diagnosed)

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References

1. Hashemi N, Boskabady MH, Nazari A. Occupational exposures and obstructive lung disease: A case-control study in hairdressers. Respiratory Care. 2010;55:895–900.

2. Mendes A, Madureira J, Neves P, Carvalhais C, Laffon B, Teixeira JP. Chemical exposure and occupational symptoms among Portuguese hairdressers. Journal of Toxicology and Environmental Health Part A. 2011;74:993–1000.

3. Nemer M, Sikkeland LIB, Kasem M, Kristensen P, Nijem K, Bjertness E, et al. Airway inflammation and ammonia exposure among female Palestinian hairdressers: A cross-sectional study. Occupational and Environmental Medicine. 2015;72:428–34.

4. Pexe ME, Marcante A, Luz MS, Fernandes PHM, Neto FC, Sato APS, et al. Hairdressers are exposed to high concentrations of formaldehyde during the hair straightening procedure. Environmental Science and Pollution Research International. 2019;26:27319–29.

5. Foss-Skiftesvik MH, Winther L, Johnsen CR, Søsted H, Mosbech HF, Zachariae C, et al. High occurrence of rhinitis symptoms in hairdressing apprentices. International Forum of Allergy & Rhinology. 2017;7:43–9.

6. Hassan OM, Bayomy H. Occupational Respiratory and Musculoskeletal Symptoms among Egyptian Female Hairdressers. Journal of Community Health. 2015;40:670–9.

7. IARC. Some Aromatic Amines, Organic Dyes, and Related Exposures. Lyon; 2010.

8. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Shekelle P, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: Elaboration and explanation. BMJ. 2015;349:g7647.

9. Anon. CRD's guidance for undertaking reviews in health care, 2009. University of York; 2009.

10. Pluye P, Gagnon M-P, Griffiths F, Johnson-Lafleur J. A scoring system for appraising mixed methods research, and concomitantly appraising qualitative, quantitative and mixed methods primary studies in Mixed Studies Reviews. International Journal of Nursing Studies. 2009;46:529–46.

11. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ. What is "quality of evidence" and why is it important to clinicians? BMJ : British Medical Journal. 2008;336:995–8.

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Appendix A: Substance identifiers

p-Phenylenediamine (INCI)

Additional CAS numbers include salts, including the sulfate. Shorthand is **PPD**.

- p-Phenylenediamine
- PPD
- 1,4-Benzenediamine
- (4-Aminophenyl)amine
- 1,4-Diaminobenzene
- 1,4-Phenylenediamine
- 4-Aminoaniline
- 4-Phenylenediamine
- C.I. 76060
- C.I. Developer 13
- C.I. Oxidation Base 10
- Paramine
- p-Aminoaniline
- p-Benzenediamine
- p-Diaminobenzene
- 106-50-3
- 624-18-0
- p-Phenylenediamine sulfate
- 16245-77-5

Toluene-2,5-diamine (INCI)

Salt, sulfate predominantly, also included. Shorthand **PTD**.

- Toluene-2,5-diamine
- 1,4-Benzenediamine, 2-methyl-
- 2-Methyl-1,4-benzenediamine
- 1,4-Diamino-2-methylbenzene
- 1-Methyl-2,5-diaminobenzene
- 2,5-Diaminotoluene
- 2,5-Diaminotoluol
- 2-Methyl-1,4-phenylenediamine
- 2-Methyl-p-phenylenediamine
- 4-Amino-2-methylaniline
- 4-Amino-3-methylaniline

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- C.I. 76042
- Toluylene-2,5-diamine
- p-Toluenediamine
- 95-70-5
- Toluene-2,5-diamine sulfate
- 615-50-9

2-Methoxymethyl-*p*-phenylenediamine (INCI)

Shorthand: **mePPD**.

- 2-Methoxymethyl-p-phenylenediamine
- 337906-36-2
- 2-Methoxymethyl-PPD
- 1,4-Benzenediamine, 2-(methoxymethyl)
- 1,4-Benzenediamine, 2-(methoxymethyl)-, sulfate
- 337906-37-3
- 2-(Methoxymethyl)-1,4-benzenediamine
- 1,4-Diamino-2-(methoxymethyl)benzene
- 2-Methoxymethyl-1,4-benzenediamine
- 2-Methoxymethyl-1,4-diaminobenzene
- 2-Methoxymethyl-1,4-phenylenediamine

Ammonium persulfate (INCI)

Shorthand: **APS**.

- Ammonium persulfate
- 7727-54-0
- Peroxydisulfuric acid ([(HO)S(O)_2]_2O_2), diammonium salt (8CI,9CI)
- Ammonium peroxidodisulfate
- Ammonium peroxydisulfate
- Ammonium peroxydisulfate ((NH_4)_2S_2O_8)
- Ammonium peroxysulfate
- Bis(ammonium) peroxodisulfate
- Diammonium peroxydisulfate
- Diammonium peroxydisulphate
- Diammonium persulfate

Potassium persulfate (INCI)

Shorthand: **PPS**.

- Potassium persulfate
- 7727-21-1

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- Peroxydisulfuric acid ([(HO)S(O)_2]_2O_2), dipotassium salt (9CI)
- Dipotassium peroxodisulfate
- Dipotassium peroxydisulfate
- Dipotassium persulfate
- Potassium dipersulfate
- Potassium peroxydisulfate
- Potassium peroxydisulfate (K_2(S_2O_8))
- Potassium peroxydisulphate

Sodium persulfate (INCI)

Shorthand: **SPS**.

- Sodium persulfate
- 7775-27-1
- Peroxydisulfuric acid ([(HO)S(O)_2]_2O_2), disodium salt (8CI,9CI)
- Sodium peroxydisulfate (6CI)
- Disodium peroxodisulfate
- Disodium peroxydisulfate
- Disodium persulfate
- Sodium dipersulfate
- Sodium peroxodisulfate
- Sodium peroxydisulfate (Na_2S_2O_8)
- Sodium persulfate (Na_2S_2O_8)

Glyceryl thioglycolate (INCI)

Shorthand: **GMTG**. Annex III/2b.

- glyceryl thioglycolate
- glyceryl monothioglycolate
- 30618-84-9
- Acetic acid, mercapto-, ester with glycerol (6CI)
- Acetic acid, mercapto-, monoester with 1,2,3-propanetriol (9CI)
- Acetic acid, mercapto-, monoester with glycerol (8CI)
- Glycerol monomercaptoacetate

Ammonium thioglycolate (INCI)

Shorthand: **ATG**. Annex III/2a.

- Ammonium thioglycolate
- 5421-46-5
- Acetic acid, mercapto-, monoammonium salt (8CI,9CI)
- Ammonium mercaptoacetate

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- Ammonium thioglycollate
- Thioglycolic acid ammonium salt

2-Hydroxyethyl methacrylate (INCI)

Shorthand: **HEMA**.

- 2-Hydroxyethyl methacrylate
- 868-77-9
- HEMA
- Methacrylic acid, 2-hydroxyethyl ester (6CI,8CI)
- Methacrylic acid, ester with glycol (7CI)
- 2-(Methacryloyloxy)ethanol
- 2-HEMA
- 2-Hydroxyethyl 2-methylprop-2-enoate
- Ethylene glycol methacrylate
- Ethylene glycol monomethacrylate
- Glycol methacrylate
- Glycol monomethacrylate
- β-Hydroxyethyl methacrylate

Ethyl cyanoacrylate

Shorthand: **ECY**.

- Ethyl cyanoacrylate
- 7085-85-0
- Acrylic acid, 2-cyano-, ethyl ester (6CI,7CI,8CI)
- 2-Cyano-2-propenoic acid ethyl ester
- 2-Cyanoacrylic acid ethyl ester
- Ethyl 2-cyanoacrylate
- Ethyl 2-cyanopropenoate
- Ethyl α-cyanoacrylate

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Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2,8
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	9

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Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	8
Support			
Sources	#5a	Indicate sources of financial or other support for the review	9
Sponsor	#5b	Provide name for the review funder and / or sponsor	9
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	9
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	3
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4, Tab. 1
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	5-7, Appendix A
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7

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Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7,8
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7,8
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8, Tab. 3
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	8
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	8
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	n/a
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8

Notes:

- 10: 5-7, Appendix A The PRISMA-P elaboration and explanation paper is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist was completed on 24. February 2021 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

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BMJ Open

Protocol for a systematic review on systemic and skin toxicity of important hazardous hair and nail cosmetic ingredients in hairdressers

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Protocol for a systematic review on systemic and skin toxicity of important hazardous hair and nail cosmetic ingredients in hairdressers

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Abstract

Introduction

Hairdressers constitute a major subgroup in the service sector. They are exposed to various substances hazardous for skin, airways, or systemically. Accordingly, skin and other occupational diseases are common. The present systematic review will compile and appraise evidence regarding skin, systemic and airways toxicity of an indicative set of specific, important product ingredients. Additionally, evidence concerning hand eczema morbidity among hairdressers will be reviewed.

Methods and analysis

Systematic searches will be performed in 2 electronic literature databases (Medline, Web of Science–Core Collection), the Cochrane register and two collections of toxicological dossiers (SCCS/EU and German MAK Commission). Additional literature sources will be retrieved using hand search of reference lists of included studies and snowballing methods. We will include studies with all types of quantitative study designs, including results from *in vitro* and *in vivo* experiments, chemical analysis, epidemiological findings, and clinical results. We will assess the risk of bias within studies amalgamating an abbreviated version of the MMAT appraisal, basic Cochrane criteria, and US EPA assessment factors for scientific information. As we expect large heterogeneity in methods and outcomes, we will conduct a narrative synthesis of results instead of a meta-analysis, except where quantitative pooling is feasible.

Ethics and dissemination

Ethical approval and patient consent are not required as this is a systematic review based on published studies. The results of this study will be published in international peer-reviewed journals.

Prospero registration number

CRD42021238118

Keywords:

systematic review, hairdressers, occupational diseases, workers' health, skin diseases, airways disorders, systemic toxicity

Article summary (strengths and limitations of this study)

- Exhaustive search for relevant studies in the most relevant databases and through additional literature sources.
- This review is not limited to specific study designs or participant groups.
- Due to expectedly very heterogeneous methods and outcomes, we will have mostly to undertake narrative synthesis instead of meta-analysis.

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[3]

Introduction

The hairdressing sector in the EU is dominated by small- and micro-businesses with some 400,000 salons employing over 1.5 million workers, which amounts to approx. 10% of the total service sector in Europe. In order to ensure good health conditions within the workforce and subsequently avoid a loss of working hours, health and safety are crucial issues. In everyday work, hairdressers are in contact with many hazardous and toxic agents, which entails different occupational health risks such as skin damage, respiratory problems, reproductive disorders, various forms of cancer, etc. Additionally, evidence concerning the morbidity of hand eczema among hairdressers will be reviewed.

Research has shown that up to 70% of hairdressers suffer from work-related skin damage, mostly hand dermatitis, at some point during their career. The most important risk factors for developing occupational skin diseases (OSD) are wet work and occupational contact to irritants, as for example detergents or hairdressing chemicals, and allergens. In Europe, OSD represent up to 35% of all reported occupational diseases, and the often chronic course causes extensive suffering for the affected workers. The economic burden of OSD in the EU exceeds € 5 billion p.a., spent on treatment, compensation, and loss of productivity. The chronic course of OSD, mainly irritant and allergic contact dermatitis of the hands, may result in detrimental socio-economic consequences, e.g. job loss and long-term unemployment.

Other occupational health problems of hairdressers are respiratory disorders related to inhalation exposure to hazardous chemicals from the used products, e.g. hair sprays. Aerosols are widely encountered in hairdressing and may reach the lungs, depending on particle size. Bleaches and hair sprays are emphasized by hairdressers as the most irritative substances for airways at their workplace.[1] Ammonia is an irritating chemical present in the air of hairdressing salons during bleaching or perm procedures, often in concentrations exceeding occupational exposure limits, as is formaldehyde during hair straightening procedures.[2–4] According to epidemiological evidence, hairdressers and hairdressing apprentices are prone to irritation of the upper airways, reporting symptoms of watery nose, nasal congestion, and cough in higher proportions than control subjects unexposed to chemical irritants.[5,6]

EU cosmetics legislation restricts the use of carcinogenic, mutagenic, or toxic for reproduction (CMR) substances. Exceptions to this general rule are possible subject to the conditions laid down in Article 15 of the Cosmetics Regulation EU 1223/2009. For example, a substance classified in category 2 may be used in cosmetic products where the substance has been evaluated by the Scientific Committee on Consumer Safety (SCCS) and found safe for use in cosmetic products. However, professionals are qualitatively and quantitatively much more exposed to such substances than a typical consumer or client. As one example, hairdressers apply colour about 6 times a day with their hands – which might already be previously damaged by occupational skin strains – being exposed, sufficiently protected or not by gloves, as opposed to consumers who apply on average once every 4 weeks a permanent colouring, exposing both hands and scalp. The specific professional exposure is normally not assessed in SCCS opinions, even though special aspects may be mentioned and referred to the Risk Assessment Committee. Thus, safety concerns related to occupational exposure remain. Indeed, in a monograph published in 2010, the International Agency for

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Research on Cancer (IARC) confirmed that the occupational exposure of hairdressers should be considered as probably carcinogenic (IARC group 2A)[7]. A new strategy for chemicals are currently being developed in EU (https://ec.europa.eu/environment/strategy/chemicals-strategy_en) making a compilation of evidence especially relevant. Hence, in the context of the project "Promoting the autonomous implementation of the European framework agreement on occupational health and safety in the hairdressing sector," a series of systematic reviews will be performed, the methods of which are described in the present publication.

Methods and analysis

Patient and public involvement

Patients and/or the public were not involved in the development of this research project; however, stakeholders from the occupational insurance and employers and employees' associations, respectively, have provided input regarding the scope of substances to assess.

Design

This study will be a systematic review with primarily narrative data synthesis and will be based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) checklist.[8] In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

Eligibility criteria

Eligibility criteria for studies to be included in the systematic review are reported following the PECOS scheme adapted from (University of York 2009, [9]) in table 1.

The scope of the systematic review, while focusing on workers in the hairdressing trade, is not limited to this particular subgroup, that is, clinical studies illustrating exposure to, and morbidity from, chemicals in hair cosmetics in other groups will be considered, too. The focus of this systematic review is on a quantitative assessment of the morbidity in terms of skin toxicity (mostly contact allergy) and systemic toxicity (e.g. CMR; see table 1) in humans as well as on *in vivo* and *in vitro* results regarding these respective toxicological endpoints. Furthermore, the overall morbidity of hand eczema among hairdressers will be quantified. We will include all types of studies with quantitative empirical data (see Table 1). Observational studies are likely to be the most important source of information for this review, supplemented by basic research evidence derived from *in vivo* and *in vitro* methods.

Target substances

Following deliberations within the project consortium and following the proposed potentially problematic types of products considered in this project (Table 2), a DELPHI survey was held shortlisting altogether 33 substances. Feed-back was provided by 48 of 121 experts and stakeholders invited (response: 39.7 %). After initial candidates had been removed as they were regarded as irrelevant for the purpose, and additional entries had been added, the remaining above-threshold candidates were eventually consented by the research consortium and finally included in the list of substances to be considered, shown in Table 2.

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Searches

We will conduct systematic searches using the following electronic databases: Pubmed/Medline and Web of Science–Core Collection (WoS). Additionally, the Cochrane registry, and the archive of scientific opinions of the Scientific Committee on Consumer Safety (SCCS) of the European Commission and its predecessors will be searched for studies, reviews and opinions (the latter normally concluding on data submitted by industry concerning the safety of a cosmetic ingredient; https://ec.europa.eu/health/scientific_committees/consumer_safety_en, last accessed 10 Feb. 2021). As far as available, dossiers in English language of the German "MAK Commission" on the substances available will be identified and used in the synopsis and discussion of results (https://onlinelibrary.wiley.com/doi/book/10.1002/3527600418, last accessed 10 Feb. 2021). All searches will be performed at the very start of the project, by 2021-03-01. Furthermore, we will hand search the bibliographies of all studies identified through the electronic database search and meeting the inclusion criteria. We will also perform forward-snowballing by using the six most important references identified, and check all references citing any of these publications. This citation analysis will be performed based on the WoS database.

Concerning those substances where an abundance of data exists on any one of the toxicological endpoints which has been summarised adequately in the past, only literature published since then will be searched for. We will use English search terms only. Generally, title, abstract and key words will be the items to be searched.

The searches are composed of the following modules: (i) substance identifiers ("SUB"), (ii) skin toxicity endpoints ("SKIN"), and (iii) systemic/respiratory toxicity endpoints ("SYS") which are defined below. Moreover, the searches will be split into the following topics, using the same set of substance identifiers as common denominator:

- "SUB" AND "SKIN": this, and the following, combination will be used to identify all studies contributing evidence to the endpoints, whether or not related to exposure as hairdresser
- "SUB" AND "SYS": as above

SUB

Substance identifiers include all relevant MeSH terms and important synonyms. The latter include the preferred chemical (IUPAC) name as well as the INCI (International Nomenclature of Cosmetic Ingredients) term, along with CAS no. and synonyms – but excluding trademarks – identified in the CAS database (SciFinder™). The substance identifiers are shown in the online supplemental **appendix A**. In order to increase the sensitivity of the search, at some expense on its specificity, product (group) descriptors are additionally employed in the search for relevant substances, joined by an OR operator, and "hairdress*" as reference to "hairdressing products," but also to the job title, as shown below. Pilot searches in Medline of the suggested terms combined with "contact AND dermatitis" (CD) and "contact AND allergy" (CA), respectively, yielded meaningful results; the number of references is indicated in parentheses after each search string:

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- hairdress* (n=305 along with CD, n=228 with CA, resp.)
- hair dyeing (n=48 along with CD, n=44 with CA, resp.)
- hair coloring (n=193 along with CD, n=153 with CA, resp.)
- permanent wave (n=30 along with CD, n=18 with CA, resp.)
- acid perm (n=1 along with CD, n=1 with CA, resp.)
- persulfate* (n=57 along with CD, n=48 with CA, resp.)
- persulphate* (n=15 along with CD, n=10 with CA, resp.)

SKIN

Endpoint / disease identifiers include the relevant MeSH terms and common medical language synonyms listed below:

Allergens[MeSH] OR Haptens[MeSH] OR agents, contact sensitizing[MeSH] OR allergic OR Dermatitis, Allergic Contact[MeSH] OR Dermatitis, Contact[MeSH] OR contact allergy OR Skin Tests[MeSH] OR Local Lymph Node Assay[MeSH] OR guinea pig maximization test OR Patch Tests[MeSH] OR Skin Irritancy Tests[MeSH] OR contact dermatitis OR contact urticaria OR contact sensitization OR Occupational Diseases[MeSH] OR work related

SYS

Endpoint / disease identifiers include the relevant MeSH terms and common medical language synonyms listed below:

Allergens[MeSH] OR Irritants[MeSH] OR allergic OR irritative OR Respiration Disorders[MeSH] OR respiratory OR Inhalation[MeSH] OR Rhinitis[MeSH] OR Asthma OR Neoplasms[MeSH] OR cancer OR Carcinogens[MeSH] OR Biomarkers, Tumor[MeSH] OR Carcinogenicity Tests[MeSH] OR Mutagens[MeSH] OR Mutagenicity Tests[MeSH] OR genotoxicity OR Reproductive Health[MeSH] OR reproductive toxicity OR reprotoxic OR Pregnancy Outcomes[MeSH] OR Pregnancy Complications[MeSH] OR Pregnancy[MeSH] OR Infertility[MeSH] OR Congenital Abnormalities[MeSH] OR birth defect OR congenital malformations OR Abortion, Spontaneous[MeSH] OR Developmental Disabilities[MeSH] OR developmental toxicity OR Menstruation Disturbances[MeSH] OR Spermatogenesis[MeSH] OR Fertility[MESH] OR Fecundability OR Time to pregnancy OR low birth weight OR Endocrine Disruptors[MeSH] OR Endocrine System Diseases[MeSH] OR Toxicity Tests[MeSH] OR Toxicity Tests, Acute[MeSH] OR Toxicity Tests, Subacute[MeSH] OR Toxicity Tests, Chronic[MeSH] OR Toxicity Tests, Subchronic OR dermal absorption OR Occupational Diseases[MeSH] OR work related OR hairdresser* OR hairdressing

Hand eczema

To identify studies concerning the morbidity of hand eczema among hairdressers, the following search, combining free text and MeSH terms will be used:

((Hairdresser* OR Hairdressing apprentice*)
AND
(“Dermatitis”[MeSH] OR Dermatitis OR “hand eczema” OR “contact allergy” OR “allergic contact dermatitis” OR “irritant contact dermatitis” OR “occupational dermatitis” OR “skin”[MeSH])

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[7]

AND
("Morbidity"[MeSH] OR "Risk"[MeSH] OR prevalence OR incidence OR Hazard OR consequences OR severity))

Further restraints

Only accepted publications newer than 1999 (i.e., 2000-01-01 and following) will be considered in the systematic search and work-up, thereby relying on up-to-date methodological standards and testing guidelines (e.g. the degree of patch test standardization achieved by the millennium; OECD Guidelines for testing of chemicals for sensitization and CMR). Moreover, it appears important to refer to risk related to current exposures, with at least partially improved cosmetic product safety, e.g. regarding permissible use levels of hazardous substances in hair dyes and other safety measures implemented by the EU Cosmetics Regulation (1223/2009/EC) or other pertinent regulations (e.g., use of bleach pastes instead of powders reducing airborne exposure to persulfate salts). Notwithstanding, reviews and scientific dossiers (such as from SCCS and predecessors, and the MAK Commission) based on previous literature will be considered in the discussion to achieve a complete appraisal of toxicological effects within scope.

Data management

For one search query (e.g. skin toxicity), the search results will be exported from Medline and WoS in a suitable format and imported into Zotero libraries, documenting the number of references contributed by each ex-/import set. In the Zotero library, bibliographical duplicates will be identified and the entry including less information (e.g., no abstract) be discarded. Each entry will be identified by a unique, human readable ID generated by using the BetterBibtex Plug-in, with manual editing where necessary. The remaining unified library will be exported in RIS format and imported into a new Rayyan project (Rayyan QCRI, https://rayyan.qcri.org/welcome, last accessed 21 Feb. 2021) for shared screening by two reviewers for eligibility based on title, key words and abstract. In case of discordant results, the entry will be reviewed by a third experienced reviewer and a final decision be made. Finalisation is expected by 2021-03-31. Reasons for non-inclusion will be documented, and summarised at the end for use in the PRISMA-P flowchart.

Study selection

The final set of references deemed eligible for full text screening by above-mentioned two reviewers will be exported from Rayyan in Bibtex format for import into the Zotero cloud-based reference database, after the initial set of references has been archived. Zotero offers freely definable "tags" for entries. These will be used to identify which of the selected substance(s) is/are treated in the article (see shorthands for substances in Table 2); these tags will be added when scrutinising and extracting the full text articles, again, independently by two reviewers, with a third senior reviewer consensualising divergent results between the two initial reviewers. All decisions and reasons leading to the exclusion of studies at this stage will be documented, providing information on the individual assessments by both initial reviewers and the final decision. At the end of this process, a set of full text articles to be included in the systematic review will be identified.

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Data extraction

Two reviewers will independently extract the data from studies meeting the inclusion criteria using standardised, pre-piloted publication record forms (PRFs). There will be different PRFs, owing to the different methodology and outcomes generated, according to study type. Thereby, one form each will be used for (i) clinical patch test studies, (ii) other observational studies addressing respiratory and systemic diseases, (iii) experimental (*in vivo* and *in vitro*) studies, and (iv) morbidity of hand eczema. A third senior reviewer will review the extracted data and make final decisions in contradictory cases. The following basic data will be extracted for observational studies: Publication ID, year of study execution, country of origin, study design, methods, study setting and population involved, information on basic characteristics of participants (eg, age, gender, ethnicity), number of participants, number of positive outcome(s), and funding source. For experimental studies, publication ID, year of study execution, country of origin, study design, methods, study setting, test system/animals, number of observational units, outcomes (mean and spread), and funding source will be documented. Outcomes will be extracted in subcategories as defined in Table 3 to enable meaningful data synthesis and analysis. Finalised PRFs (expected by mid-May 2021) will be preserved and published as supplemental material to the systematic review.

If necessary, outcome information will be approximated from figures in the reports. If more than one publication reports on the same study we will combine information from the publications if they report on different outcomes and use the more comprehensive one(s) if the shorter one(s) do(es) not add any additional information. If any contradictions with regards to content appear between such multiple publications, we will extract the information given in the more recent publication. We will contact study authors by email if important methodological details are missing.

Risk of bias within included studies and quality of evidence assessment

Suitable criteria for assessing risk of bias and quality of evidence will be applied. Two reviewers will independently appraise studies meeting the inclusion criteria after full text scrutiny without being blinded to the studies. The published MMAT appraisal will be used on the study level in case of homogeneous methodology, and on the outcome level in case of multiple methodologies used in one study.[10] Moreover, information and selection bias will be examined following basic Cochrane collaboration recommendations [11], and further criteria relating to scientific validity as elaborated by a working group of the US EPA[12] will be included in the risk of bias assessment tool amalgamated from these three resources.

Data synthesis and analysis

There will be substantial heterogeneity both in methodologies (even in the sub-categories of “experimental” and “clinical” research) and in outcomes. Instead of a meta-analysis, we will primarily conduct a narrative synthesis following guidance from the Centre for Reviews and Dissemination.[9] Summary tables will present the main characteristics of the included studies, their finding as well as their quality rating. Notwithstanding, if for a subset of eligible studies a quantitative summary appears feasible, in view of sufficiently uniform methodology and outcome definition, graphical summaries as Forest plots with an assessment of heterogeneity (I^2) will be presented. In such cases, the strength of cumulative

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evidence will be assessed using the GRADE criteria.[13] Apart from a results presentation evidently stratified for the substances concerned, subgroup analyses or meta regression approaches are not foreseen.

Ethics and dissemination

Ethical approval and patient consent are not required as this is a systematic review based on published studies. This systematic review has been registered in PROSPERO (CRD42021238118). The results of this review will be published in international peer-reviewed journals.

Protocol amendments

This is the initial version of the study protocol. Amendments to the protocol will be filed with PROSPERO and listed in the results publication(s), which will otherwise refer to the present publication.

Author Contributions (CRediT)

Wolfgang Uter: Conceptualization, Methodology, Resources, Writing - Original Draft; **Jeanne D. Johansen:** Conceptualization, Methodology, Writing - Review & Editing; **Martin S. Havmose:** Conceptualization, Writing - Review & Editing; **Sanja Kezic:** Conceptualization, Methodology, Writing - Review & Editing; **Henk F. van der Molen:** Methodology, Writing - Review & Editing; **Jelena Macan:** Conceptualization, Methodology, Writing - Review & Editing; **Rajka Turk:** Conceptualization, Methodology, Writing - Review; **Željka Babić:** Conceptualization, Methodology, Writing – Review; **Cara Symanzik:** Conceptualization, Methodology, Writing - Review; **Swen M. John:** Conceptualization, Methodology, Writing - Review & Editing, Project administration, Funding acquisition, Guarantor of the review. All authors have read and approved the final submitted version of the manuscript.

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This research is supported by a grant from Uni Europa–The European Global Services Union (Project VS/2019/0440: “Promoting the autonomous implementation of the European framework agreement on occupational health and safety in the hairdressing sector”). Other than being given the opportunity to provide input in the initial Delphi process to identify relevant substances, the sponsor has no role in the development of the protocol, nor in the performance of the systematic review and the publication of its results.

Conflict of interests

W.U. has received a honorarium for a lecture on contact allergy from mixed dermatopharmaceutical sponsors (GEIDAC, Toledo, Sept. 2018) and travel reimbursement for participation in study meetings of the IDEA project (IFRA). W.U. is external expert for the SCCS. Other authors: None to declare. Provenance and peer review: Not commissioned; externally peer reviewed.

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[10]

Data statement

Not applicable (no original data).

Acknowledgments

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[11]

Table 1: Eligibility criteria following the PECOS scheme, adapted from (University of York 2009)[9]

Criterion	Inclusion	Exclusion
Participants	Hairdressers, patients, cosmetic products	None
Exposure	Exposure to (an) eligible chemical(s)	N/A
Comparator	Clients, consumers, normal population (no, or less, exposure)	N/A
Outcome	Skin toxicity event (contact allergy, irritancy)	N/A
	Systemic toxicity (CMR, ED, respiratory)	N/A
Study design	Experimental studies, e.g.	Qualitative studies
	Chemical analyses	
	in vivo Toxicological studies	
	in vitro Toxicological studies	
	Observational studies, e.g.	
	Case–control studies	
	Prospective and retrospective cohort studies	
	(Repeated) cross-sectional studies	
	Case reports, clinical series	

CMR, carcinogenicity/mutagenicity/reproductive toxicity; ED, endocrine disruption; N/A, not applicable.

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[12]

Table 2: List of most relevant product groups in hairdressing with substances finally included into the systematic review

	Product category	Substance(s)
1	Oxidative hair dyes/colorants	*p*-Phenylenediamine (PPD; CAS no. 106-50-3) and its salts (CAS no. 624-18-0, 16245-77-5), toluene-2,5-diamine (PTD; CAS no. 95-70-5) and its sulphate (CAS no. 615-50-9), 2-Methoxymethyl-PPD (mePPD; CAS no. 337906-36-2)
2	Bleaches	Persulfate salts: ammonium, APS, CAS no. 7727-54-0; potassium, PPS, CAS no. 7727-21-1; sodium, SPS, CAS no. 7775-27-1
3	Perms and relaxing substances	Salts and esters of thioglycolic acid: glyceryl thioglycolate (GMTG; CAS no. 30618-84-9), ammonium thioglycolate (ATG; CAS no. 5421-46-5)
4	Cosmetic glues	2-Hydroxyethyl methacrylate (HEMA; CAS no. 212-782-2), ethyl cyanoacrylate (ECY; CAS no. 7085-85-0)

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[13]

Table 3: Subcategories of outcomes

- Skin toxicity
  - Skin sensitisation / contact allergy in humans (e.g., numbers tested, numbers positive, test methods)
  - Skin irritation in humans (e.g., exposure conditions leading to irritation)
  - Sensitisation *in vivo* or *in vitro* (e.g., guideline vs. non-guideline method, main read-out such as EC3-value for LLNA)
  - Irritancy *in vivo* or *in vitro* (e.g., guideline vs. non-guideline method, main read-out)
- Systemic toxicity
  - Carcinogenicity/cancer risk in humans (e.g., epidemiological studies on occupational vs. consumer exposure)
  - Carcinogenicity *in vivo* or *in vitro* (e.g., mechanistic studies, tumour promoting activity and frequency of tumour incidence)
  - Mutagenicity *in vivo* or *in vitro* (e.g., genotoxicity tests, main read-out)
  - Reproductive and developmental toxicity in humans (e.g., menstrual disorders, sperm production, pregnancy and birth outcomes)
  - Reproductive and developmental effects in vivo (e.g., male and female reproductive effects, developmental and post-natal toxicity)
  - Endocrine disruption *in vivo* or *in vitro* (e.g. test methods, adverse effects on endocrine relevant endpoints, endocrine/androgen/thyroid/steroidogenesis)
- Respiratory toxicity
  - Airways sensitization and irritation in humans (e.g. inhalatory exposure, inhalatory allergens, respiratory irritants, asthma, rhinitis, occupational diseases) and animal models
- Hand eczema
  - Hairdresser/hairdressing apprentice
  - Gender
  - Morbidity (prevalence, incidence)
  - Debut (onset)
  - Severity/frequency of eruptions
  - Concomitant atopic dermatitis
  - Diagnosis (self-reported vs. physician diagnosed)

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References

1. Hashemi N, Boskabady MH, Nazari A. Occupational exposures and obstructive lung disease: a case-control study in hairdressers. *Respir Care*. 2010;55(7):895-900.

2. Mendes A, Madureira J, Neves P, Carvalhais C, Laffon B, Teixeira JP. Chemical exposure and occupational symptoms among Portuguese hairdressers. *J Toxicol Environ Health A*. 2011;74(15-16):993-1000. doi:10.1080/15287394.2011.582027

3. Nemer M, Sikkeland LIB, Kasem M, et al. Airway inflammation and ammonia exposure among female Palestinian hairdressers: a cross-sectional study. *Occup Environ Med*. 2015;72(6):428-434. doi:10.1136/oemed-2014-102437

4. Pexe ME, Marcante A, Luz MS, et al. Hairdressers are exposed to high concentrations of formaldehyde during the hair straightening procedure. *Environ Sci Pollut Res Int*. 2019;26(26):27319-27329. doi:10.1007/s11356-019-05402-9

5. Foss-Skiftesvik MH, Winther L, Johnsen CR, et al. High occurrence of rhinitis symptoms in hairdressing apprentices. *Int Forum Allergy Rhinol*. 2017;7(1):43-49. doi:10.1002/alr.21834

6. Hassan OM, Bayomy H. Occupational Respiratory and Musculoskeletal Symptoms among Egyptian Female Hairdressers. *J Community Health*. 2015;40(4):670-679. doi:10.1007/s10900-014-9983-y

7. IARC. *Some Aromatic Amines, Organic Dyes, and Related Exposures*. Vol 99.; 2010. Accessed February 8, 2021. https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Some-Aromatic-Amines-Organic-Dyes-And-Related-Exposures-2010

8. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ*. 2015;349:g7647. doi:0.1136/bmj.g7647

9. Anon. *CRD's Guidance for Undertaking Reviews in Health Care, 2009.*; 2009.

10. Pluye P, Gagnon M-P, Griffiths F, Johnson-Lafleur J. A scoring system for appraising mixed methods research, and concomitantly appraising qualitative, quantitative and mixed methods primary studies in Mixed Studies Reviews. *Int J Nurs Stud*. 2009;46(4):529-546. doi:10.1016/j.ijnurstu.2009.01.009

11. Sterne JAC, Hernán MA, McAleenan A, Reeves BC, Higgins JPT. Chapter 25: Assessing risk of bias in a non-randomized study. In: *Cochrane Handbook for Systematic Reviews of Interventions*. 6.1. The Cochrane Collaboration; 2020.

12. Anon. *A Summary of General Assessment Factors for Evaluating the Quality of Scientific and Technical Information - Prepared for the U.S. Environmental Protection Agency by*

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Members of the Assessment Factors Workgroup, a Group of the EPA's Science Policy Council. US EPA; 2003.

13. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ. What is "quality of evidence" and why is it important to clinicians? *BMJ*. 2008;336(7651):995-998. doi:10.1136/bmj.39490.551019.BE

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Appendix A: Substance identifiers

p-Phenylenediamine (INCI)

Additional CAS numbers include salts, including the sulfate. Shorthand is **PPD**.

- *p*-Phenylenediamine
- PPD
- 1,4-Benzenediamine
- (4-Aminophenyl)amine
- 1,4-Diaminobenzene
- 1,4-Phenylenediamine
- 4-Aminoaniline
- 4-Phenylenediamine
- C.I. 76060
- C.I. Developer 13
- C.I. Oxidation Base 10
- Paramine
- *p*-Aminoaniline
- *p*-Benzenediamine
- *p*-Diaminobenzene
- 106-50-3
- 624-18-0
- *p*-Phenylenediamine sulfate
- 16245-77-5

Toluene-2,5-diamine (INCI)

Salt, sulfate predominantly, also included. Shorthand **PTD**.

- Toluene-2,5-diamine
- 1,4-Benzenediamine, 2-methyl-
- 2-Methyl-1,4-benzenediamine
- 1,4-Diamino-2-methylbenzene
- 1-Methyl-2,5-diaminobenzene
- 2,5-Diaminotoluene
- 2,5-Diaminotoluol
- 2-Methyl-1,4-phenylenediamine
- 2-Methyl-p-phenylenediamine
- 4-Amino-2-methylaniline

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- 4-Amino-3-methylaniline
- C.I. 76042
- Toluylene-2,5-diamine
- *p*-Toluenediamine
- 95-70-5
- Toluene-2,5-diamine sulfate
- 615-50-9

2-Methoxymethyl-*p*-phenylenediamine (INCI)

Shorthand: **mePPD**.

- 2-Methoxymethyl-p-phenylenediamine
- 337906-36-2
- 2-Methoxymethyl-PPD
- 1,4-Benzenediamine, 2-(methoxymethyl)
- 1,4-Benzenediamine, 2-(methoxymethyl)-, sulfate
- 337906-37-3
- 2-(Methoxymethyl)-1,4-benzenediamine
- 1,4-Diamino-2-(methoxymethyl)benzene
- 2-Methoxymethyl-1,4-benzenediamine
- 2-Methoxymethyl-1,4-diaminobenzene
- 2-Methoxymethyl-1,4-phenylenediamine

Ammonium persulfate (INCI)

Shorthand: **APS**.

- Ammonium persulfate
- 7727-54-0
- Peroxydisulfuric acid ([(HO)S(O)_2]_2O_2), diammonium salt (8CI,9CI)
- Ammonium peroxidodisulfate
- Ammonium peroxydisulfate
- Ammonium peroxydisulfate ((NH_4)_2S_2O_8)
- Ammonium peroxysulfate
- Bis(ammonium) peroxodisulfate
- Diammonium peroxydisulfate
- Diammonium peroxydisulphate
- Diammonium persulfate

Potassium persulfate (INCI)

Shorthand: **PPS**.

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- Potassium persulfate
- 7727-21-1
- Peroxydisulfuric acid ([(HO)S(O)_2]_2O_2), dipotassium salt (9CI)
- Dipotassium peroxodisulfate
- Dipotassium peroxydisulfate
- Dipotassium persulfate
- Potassium dipersulfate
- Potassium peroxydisulfate
- Potassium peroxydisulfate (K_2(S_2O_8))
- Potassium peroxydisulphate

Sodium persulfate (INCI)

Shorthand: **SPS**.

- Sodium persulfate
- 7775-27-1
- Peroxydisulfuric acid ([(HO)S(O)_2]_2O_2), disodium salt (8CI,9CI)
- Sodium peroxydisulfate (6CI)
- Disodium peroxodisulfate
- Disodium peroxydisulfate
- Disodium persulfate
- Sodium dipersulfate
- Sodium peroxodisulfate
- Sodium peroxydisulfate (Na_2S_2O_8)
- Sodium persulfate (Na_2S_2O_8)

Glyceryl thioglycolate (INCI)

Shorthand: **GMTG**. Annex III/2b.

- glyceryl thioglycolate
- glyceryl monothioglycolate
- 30618-84-9
- Acetic acid, mercapto-, ester with glycerol (6CI)
- Acetic acid, mercapto-, monoester with 1,2,3-propanetriol (9CI)
- Acetic acid, mercapto-, monoester with glycerol (8CI)
- Glycerol monomercaptoacetate

Ammonium thioglycolate (INCI)

Shorthand: **ATG**. Annex III/2a.

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- Ammonium thioglycolate
- 5421-46-5
- Acetic acid, mercapto-, monoammonium salt (8CI,9CI)
- Ammonium mercaptoacetate
- Ammonium thioglycollate
- Thioglycolic acid ammonium salt

2-Hydroxyethyl methacrylate (INCI)

Shorthand: **HEMA**.

- 2-Hydroxyethyl methacrylate
- 868-77-9
- HEMA
- Methacrylic acid, 2-hydroxyethyl ester (6CI,8CI)
- Methacrylic acid, ester with glycol (7CI)
- 2-(Methacryloyloxy)ethanol
- 2-HEMA
- 2-Hydroxyethyl 2-methylprop-2-enoate
- Ethylene glycol methacrylate
- Ethylene glycol monomethacrylate
- Glycol methacrylate
- Glycol monomethacrylate
- β-Hydroxyethyl methacrylate

Ethyl cyanoacrylate

Shorthand: **ECA**.

- Ethyl cyanoacrylate
- 7085-85-0
- Acrylic acid, 2-cyano-, ethyl ester (6CI,7CI,8CI)
- 2-Cyano-2-propenoic acid ethyl ester
- 2-Cyanoacrylic acid ethyl ester
- Ethyl 2-cyanoacrylate
- Ethyl 2-cyanopropenoate
- Ethyl α-cyanoacrylate

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Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2,8
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	9

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Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	8
Support			
Sources	#5a	Indicate sources of financial or other support for the review	9
Sponsor	#5b	Provide name for the review funder and / or sponsor	9
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	9
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	3
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4, Tab. 1
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	5-7, Appendix A
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7

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Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7,8
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7,8
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8, Tab. 3
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	8
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	8
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	n/a
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8

Notes:

- 10: 5-7, Appendix A The PRISMA-P elaboration and explanation paper is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist was completed on 24. February 2021 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

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