

The Effect of Cyclohexanone Exposure on Incidence of Irritant Contact Dermatitis

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Abstract

Background: Skin disorders or abnormalities occur in more than 35% of all occupational disorders. Contact dermatitis is the most recognized occupational disease in many countries (with irritant contact dermatitis accounting for 80% of the cases), yet these cases are often not reported. One of the causes of irritant contact dermatitis is Cyclohexanone, a chemical recognized as an oxidizing agent that can irritate the skin. This evidence-based case report aims to gather evidence about the effect of cyclohexanone exposure on the incidence of irritant contact dermatitis.

Method: The case in this study is about a 37-year-old woman who worked as a logo printing operator in a shoe manufacturing company that is exposed to cyclohexanone and was diagnosed with irritant contact dermatitis. A literature search was conducted through PubMed, Scopus, and ProQuest and performed with the hand searching method. The inclusion criteria included systematic review study, cohort study, case-control study, cross-sectional study, irritant contact dermatitis, cyclohexanone, and occupational. Then, critically appraised using relevant criteria by the Oxford Center for Evidence-Based Medicine.

Result: Three relevant cross-sectional studies were found through literature searching and are critically appraised. The estimate's magnitude and precision regarding the association between the exposure and outcome in the first study cannot be assessed; the study only stated no statistically significant p-value in the prevalence of occupational skin dermatitis between departments and the examination between departments. The second study showed that workers with solvent chemical mixture exposure, including cyclohexane, are correlated with skin symptoms, dry or itchy skin on the hands or arms, POR 1.46 (95% CI 1.06-2.01), and redness on hands or arms, POR 1.50 (95% CI 1.09-2.70). In comparison, the third study showed that workers with a high dermal single exposure to cyclohexane have a higher risk for the incidence of hand dermatitis OR 2.15 (95% CI 0.59-7.95) without any statistical significance.

Conclusion: The available evidence from cross-sectional studies did not prove an association between cyclohexanone exposure and irritant contact dermatitis in workers; only one study shows a significant association statistically. However, it is recommended to provide tools to prevent direct contact with the chemical; workers should also wear appropriate protective gloves to avoid occupational irritant contact dermatitis. A better study design such as cohort or case-control is needed to provide substantial evidence that cyclohexanone exposure can cause irritant contact dermatitis in workers.

Keywords: Cyclohexanone, irritant contact dermatitis, occupational

Abstrak

Latar belakang: Penyakit kulit atau kelainan kulit terjadi pada lebih dari 35% dari semua kelainan akibat kerja. Dermatitis kontak adalah penyakit akibat kerja yang paling dikenal di banyak negara (dengan dermatitis kontak iritan terhitung 80% dari kasus), namun kasus-kasus ini sering tidak dilaporkan. Salah satu penyebab dermatitis kontak iritan adalah cyclohexanone, bahan kimia yang dikenal sebagai oksidator yang dapat mengiritasi kulit. Laporan Kasus Berbasis Bukti ini bertujuan untuk mengumpulkan informasi/bukti tentang pengaruh paparan cyclohexanone terhadap kejadian dermatitis kontak iritan.

Metode: Kasus dalam studi ini adalah tentang seorang wanita berusia 37 tahun yang bekerja sebagai operator pencetakan logo di sebuah perusahaan manufaktur sepatu yang terpapar cyclohexanone dan didiagnosis dengan dermatitis kontak iritan. Pencarian literatur dilakukan melalui PubMed, Scopus, dan ProQuest dan dilakukan dengan metode hand searching. Kriteria inklusi meliputi studi tinjauan sistematis, studi kohort, studi kasus-kontrol, studi potong lintang, dermatitis kontak iritan, cyclohexanone, dan pekerjaan. Kemudian, dinilai secara kritis menggunakan kriteria yang relevan dari Oxford Centre for Evidence-Based Medicine.

Hasil: Tiga studi potong lintang yang relevan ditemukan melalui pencarian literatur dan dinilai secara kritis. Besarnya perkiraan dan presisi mengenai hubungan antara paparan dan hasil dalam studi pertama tidak dapat dinilai; penelitian ini hanya menyatakan tidak ada nilai p yang signifikan secara statistik dalam prevalensi dermatitis akibat kerja antar departemen dan pemeriksaan antar departemen. Studi kedua menunjukkan bahwa pekerja dengan paparan campuran bahan kimia pelarut, termasuk cyclohexane, berkorelasi dengan gejala kulit, kulit kering atau gatal pada tangan atau lengan, POR 1,46 (95% CI 1,06-2,01), dan kemerahan pada tangan atau lengan, POR 1,50 (95% CI 1,09-2,70). Sebagai perbandingan, penelitian ketiga menunjukkan bahwa pekerja dengan paparan tunggal cyclohexane yang tinggi pada kulit memiliki risiko lebih tinggi untuk kejadian dermatitis tangan dengan nilai OR 2,15 (95% CI 0,59-7,95) tanpa signifikansi statistik.

Kesimpulan: Bukti yang tersedia dari studi potong lintang tidak membuktikan hubungan antara paparan cyclohexanone dan dermatitis kontak iritan pada pekerja; hanya satu studi yang menunjukkan hubungan yang signifikan secara statistik. Namun, disarankan untuk menyediakan peralatan kerja untuk mencegah kontak langsung dengan bahan kimia; pekerja juga harus mengenakan sarung tangan pelindung yang sesuai untuk menghindari dermatitis kontak iritan akibat kerja. Sebuah desain studi yang lebih baik seperti kohort atau kasus-kontrol diperlukan untuk memberikan bukti substansial bahwa paparan cyclohexanone dapat menyebabkan dermatitis kontak iritan pada pekerja.

Kata kunci: Cyclohexanone, dermatitis kontak iritan, pekerjaan

Introduction

Skin disorders or abnormalities occur in more than 35% of all occupational disorders.^{1,2} Contact dermatitis is the most recognized occupational disease in many countries, and cases of occupational contact dermatitis are often not reported. Because it is very common, health care providers must also be aware of this occupational disease. Contact dermatitis is a responsive inflammation of the skin that occurs immediately after contact with a substance, such as a chemical or biological compound. Contact dermatitis can be caused by direct irritation from a substance, known as irritant contact dermatitis (ICD), or contact with an unfavorable allergen, known as allergic contact dermatitis (ACD).³

Occupational contact dermatitis accounts for 90% of all work-related skin disorders. It can be divided into irritant contact dermatitis, which occurs in 80% of cases, and the rest are allergic contact dermatitis. In most cases, these two types will appear as eczematous lesions on exposed body parts, especially on the hands.⁴

The clinical symptoms of irritant contact dermatitis are a history of exposure and a temporal relationship with irritants, hands are the most common location, followed by the face and feet. Subjective symptoms include itching, burning/pain, and clinical presentation depending on the type of irritant and the pattern of exposure. It is usually accompanied by dry skin or skin barrier, the lesion will improve if exposure is stopped and is often related to the work/work environment.

Cyclohexanone is a type of chemical that is included in the group of oxidizing agents that are irritating to the skin. This substance causes mild irritation and does not cause severe skin reactions on short contact (<1 hour). Skin lesions can vary according to the type of exposure, body region, and individual vulnerability.⁶

Improper skin cleansing is a major cause of occupational irritant contact dermatitis. Therefore, handwashing methods and facilities need to be reviewed if in the workplace there are one or more cases of work-related irritant contact dermatitis. Irritating chemicals are aromatic, aliphatic, and solvent solvents, such as turpentine, alcohol, esters, and ketones. Some organic solvents produce an immediate erythematous reaction on the skin and remove lipids from the stratum corneum.⁷ This report aims to present evidence about the effect of cyclohexanone exposure on the incidence of irritant contact dermatitis in workers.

Case Description

A 37-year-old woman attended to in-house polyclinics with complaints of redness and intermittent itching on the back of the right hand and left forearm. The complaint in the right hand occurs due to chemical exposure, the patient does not routinely use chemical gloves provided by the company because of heat and discomfort when used, and itching on the left forearm is caused by scratching using the right hand. It felt repeatedly by the patient during the past year and happened when returning to work, especially on Monday-Friday, and improved when the days off. The physical examination revealed an efflorescence in the form of multiple lesions with scaly erythematous plaque, lichenification with erosions, and excoriations on the back of the right hand and left forearm.

The workplace is a shoe manufacturing factory with several work areas such as preparation, preparing/upper sole, assembling, finishing, and packing. The patient has been working in the factory for more than 10 years with a history of working in shoe packing and working in the preparing/upper sole area for the past year and being exposed to cyclohexanone every day because of cleaning logo screens.

She often sought treatment at the polyclinics and was given antihistamines, anti-inflammatory drugs, and corticosteroid ointments. Complaints decreased momentarily, but reappeared when returning to work and exposed to the chemical. This latest complaint had not improved within two weeks and finally, the patient was referred to a dermatologist and diagnosed with Irritant Contact Dermatitis.

The patient had no family history of illness or previous allergies. She only worked at the factory and did not work anywhere else or even on workdays off. Her activities at home were not exposed to chemicals, no mopping or washing clothes because she was assisted by her mother, and occasionally helped wash the dishes with liquid dishwashing soap.

Clinical Question

Does Cyclohexanone exposure cause irritant contact dermatitis?

P : Worker

I : Cyclohexanone exposure

C : -

O : Irritant Contact Dermatitis

Literature Search

A literature search was conducted to answer clinical questions through these electronic databases: PubMed, Scopus, and ProQuest. The keywords used are 'irritant contact dermatitis', 'cyclohexanone', and 'occupational'. Then a literature search is also performed with the hand searching method. The inclusion criteria of this

search strategy were systematic review, cohort study, case-control study, cross-sectional study, irritant contact dermatitis, cyclohexanone, and occupational. Exclusion criteria for these articles such as case report studies, articles without population samples, studies in animals, studies that are duplicated on other online search sites, age < 18 years, and inappropriate exposure (Figure 1). The search was done on May 17, 2020.

Table 1. Search strategies using electronic databases from PubMed, Scopus, and ProQuest

Electronic database	Search strategy	Hit	Selected
PubMed	((irritant contact dermatitis) OR (irritant contact dermatitis [MeSH Terms])) AND ((occupational [MeSH Terms]) OR (occupational)) AND ((cyclohexan*) OR (cyclohexan* [MeSH Terms]))	12	1
Scopus	irritant AND contact AND dermatitis AND occupational AND CHEMNAME (cyclohexan*)	16	0
ProQuest	(irritant contact dermatitis CI) AND occupational AND ((cyclohexan* CI) OR (cyclohexan* MeSH))	44	1

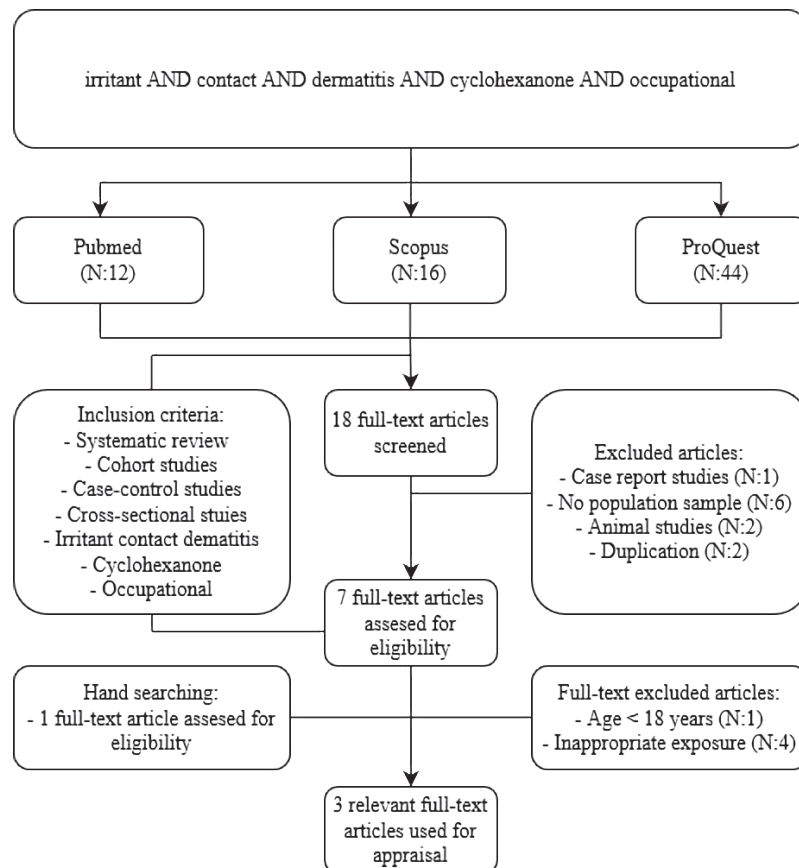


Figure 1. Literature Searching Chart

Critical Appraisal

After obtaining articles based on screening through the inclusion and exclusion criteria then these articles were critically appraised to determine whether the article is valid, important, and applicable to the patient using relevant criteria by the Oxford Center for Evidence-Based Medicine.¹¹

Results

Based on online search results, three articles were found that fit the inclusion and exclusion criteria, which are cross-sectional studies by Febriana SA et al. (2014)⁸, Todd L et al. (2008)⁹, and Vermeulen R et al. (2001)¹⁰. After the articles were critically appraised, it was concluded that all the articles were valid. The results of the critical appraisal assessment can be seen in table 2.

Table 2. Results of study characteristics and critical study

Studies	Method	Subject	Intervention	Impact and Results	The same treatment	Follow-up	Causal diagnostic test	Level of evidence *
Febriana SA et al. (2014) ⁸	A Cross-sectional study of the effects of exposure to mixed chemicals including cyclohexanone on female workers in shoe manufacturing companies in Sidoarjo	514 workers with 497 women and 17 men history of exposure to mixed chemical exposure including cyclohexanone working in the shoe manufacturing production process	Exposure to chemical sensitizers and irritants	Impact: - Effects of exposure to chemical sensitizers and irritants on the skin Results: - The prevalence of occupational skin disease is 7.6% - There were 21 employees diagnosed with irritant contact dermatitis from 435 people in the prep / upper sole, sewing preparation (skiving, embossing, embroidery, perforate, folding), gluing, and assembling which were exposed to cyclohexanone - Confirmation with the Patch test uses the European baseline series, the shoe series, and additional specific allergens for shoe companies	Yes	No	Yes	4
Todd L et al. (2008) ⁹	A Cross-sectional study about the prevalence of health symptoms due to exposure to solvent mix chemicals and the risk of ergonomic hazards to workers in four footwear companies and one shoe equipment company in Thailand	1784 workers from four footwear companies and one equipment company filled out the health questionnaire	Exposure to solvent chemical mixtures (n-hexane, toluene, methyl ethyl ketone, acetone, xylenes, ethyl acetate, hexane, cyclohexane) and the risk of ergonomic hazards	Impact: - Effects of exposure to a mixture of chemicals on the skin Results: - The results focused on the effect of solvent mixture chemical exposure - Prevalence Odds Ratio (POR) and 95% CI values from the health questionnaire on symptoms of the skin: 1. Dry or itchy skin on the hands or arms, 1.46 (1.06-2.01) 2. Redness on hands or arms, 1.50 (1.09-2.70) 3. Inflammation in the hands or arms, 1.26 (0.79-2.01)	Yes	No	Yes	4

Studies	Method	Subject	Intervention	Impact and Results	The same treatment	Follow-up	Causal diagnostic test	Level of evidence *
Vermeulen R et al. (2001) ¹⁰	A cross-sectional study of the effects of exposure to cyclohexane chemicals on worker skin, frequency of handwashing, and hand dermatitis in the rubber manufacturing industry in the Netherlands	202 male workers underwent medical evaluations, exposure surveys, and completed self-questionnaires	Cyclohexane chemical exposure	Impact: - Effects of cyclohexane chemical exposure Results: - From 202 subjects, 14 workers were diagnosed with major hand dermatitis, 28% showed symptoms of minor hand dermatitis, and 17% were diagnosed with skin trauma (traumata) - As many as 34.8% said their skin disorders were due to working conditions, and 41.6% said their skin disorders improved when they did not work for several days - Proportion of subjects claiming benefits after a few days off: 64.3% of those with major hand dermatitis, 42.9% with minor hand dermatitis, and 29.4% with traumata - Two subjects reported experiencing an allergic reaction due to contact with rubber and chemical additives	Yes	No	Yes	4

* Level of evidence (etiology)¹¹:

- 1: *Systematic review of randomized trials, a systematic review of nested case-control studies, n-of-1 trial with the patient, you are raising the question about or observational study with dramatic effects*
- 2: *Individually randomized trial or (exceptionally) observational study with dramatic effects*
- 3: *Non-randomized controlled cohorts/follow-up studies (post-marketing surveillance) provided there are sufficient numbers to rule out common harm. (For long-term harms the duration of follow-up must be sufficient)*
- 4: *Case-series, case-control, or historically controlled studies*
- 5: *Mechanism-based reasoning*

The first article is a cross-sectional study by Febriana SA et al.⁸ that observed the working process and assessed the prevalence of occupational skin diseases was conducted between January and March 2010 at a shoe factory in Sidoarjo Industrial Area, East Java, Indonesia. This shoe factory was chosen for the following reasons: it had more than 500 workers, uses modern equipment, and exported its products to leading brands in Europe, the United States, and other Asian countries. Workers are examined and interviewed using the *Nordic Occupational Skin Questionnaire-2002/LONG*

conducted by medical students and anthropologists then physical examinations of the skin by two Dermatologists who performed double-blinded examinations (without knowledge of the patient and the results of the questionnaire). Patch tests are carried out with allergens from the European baseline series, the shoe series (Chemotechnique Diagnostics, Vellinge, Sweden), and additional allergens specific to shoe companies. Patch test results were assessed on days 2,4 and 7 as recommended by the International Contact Dermatitis Research Group (ICDRG). Statistics use Chi-Square

Test to compare the difference between interview-based prevalence and examination-based prevalence and to compare the prevalence of Occupational Skin Diseases (OSD) in departments based on interviews and examinations.

Workers are exposed to cyclohexanone in the preparing/upper sole, sewing preparation (skiving, embossing, embroidery, perforate, folding), gluing, and assembling. Obtained results Occupational Skin Diseases (OSD) in shoe factories are mainly related to exposure to potential physical and chemical hazards in hot and humid environmental conditions. Of a total of 514 workers, 8.5% reported having OSD at present and 4.8% reported having a history of OSD. Occupational skin diseases were diagnosed in 29% of workers by dermatologists and 7.6% of them were occupational contact dermatitis (OCD). Of workers with contact dermatitis, 33 of them agreed to do a patch test, 14 (3%) workers showed positive results and were diagnosed with occupational allergic contact dermatitis or Occupational Allergic Contact Dermatitis (OACD), and 25 (4.9%) contact dermatitis work-related irritants or Occupational Irritant Contact Dermatitis (OICD).

The second article is also a cross-sectional study from Todd L et al.⁹, this study reports on evaluating the prevalence of health symptoms arising from exposure to mixed chemicals used in the workplace. The mixed chemical contains n-hexane, toluene, methyl ethyl ketone, acetone, xylene, ethyl acetate, hexane, and cyclohexane. Research carried out on 1784 workers from four footwear companies and one equipment company filled out a health questionnaire. The 10-page health questionnaire was first developed in English in the United States and then translated into Thai by postgraduate students and teaching staff from the Department of Health and Safety at Mahidol University in Bangkok, Thailand. The questionnaire included questions about the workers' demographics (age, sex, smoking history, education, marital status, and length of work), position, use of chemicals, use of personal protective equipment, technical controls, workplace conditions, and health outcomes. The questionnaire was designed to evaluate the health status of workers in connection with exposure to chemicals and ergonomic hazards. The symptoms' questions are based on the use of chemicals in the factory provided by the company. Symptoms are divided into six physiological categories: eye, upper respiratory system (nasopharyngeal region), lower respiratory system (pulmonary region), central

nervous system, skin, and musculoskeletal system, which give a total of 28 different symptoms. For each symptom, the workers identified whether or not they ever had any of the symptoms. For each symptom, they identified "yes before starting employment", "yes after starting employment", "yes in the last month" or "never".

Statistical tests were performed with multiple logistic regression used to calculate the adjusted prevalence odds ratio (POR) and 95% confidence interval (CI) that describe the relationship between exposure and symptoms that develop after working in the four combined shoe factories. A POR value > 1.0 indicates a positive relationship between exposure and symptoms. Age (in years), gender, smoking status (never, past or present), and pre-work symptoms (yes, no) were entered into Symptoms related to the skin have a significant relationship with chemical exposure.

The third article is a cross-sectional study from Vermeulen R et al.¹⁰, this study reports on evaluating the prevalence of skin disorders as well as the possible relationship between skin exposure and hand dermatitis. More information details are obtained from actual exposure to workers' skin, hand washing practices, individual characteristics, and domestic exposures to identify specific risk factors with a possible increase in occupational skin disorders. The research was carried out on 202 worker subjects out of 1,355 total workers. The study was conducted in January - July 1997 on rubber manufacturing industry workers in the Netherlands. The research subjects were selected randomly among the workers from nine companies (three rubber tire companies, five rubber general materials companies, and one retread company) based on production activities (compounding and mixing, pre-treating, molding, curing, finishing, shipping, engineering service, and laboratory). Subjects underwent medical evaluation, exposure surveys, and completed self-questionnaires.

This independent questionnaire contains demographic questions (age, ethnicity, etc.), risk factors for skin complaints and disease, history of atopic dermatitis, work absenteeism, and medical consultation related to skin complaints. All 202 subjects were male, aged between 19 and 60 years, with an average age of 37.6 years (standard deviation = 9.1).

Two dermatologists performed medical evaluations on the current skin condition. Their classification is based on objective skin symptoms: active hand dermatitis ("major" dermatitis), initial symptoms

of dermatitis ("minor" dermatitis), and skin trauma (traumata). Major dermatitis is defined as erythema, papules, vesicles, and fissures, a clear eczematous picture. Minor dermatitis is described as erythema, mild cracked skin, and scaly. Traumata on the skin describe lesions and burns. No distinction is made between irritant and allergic dermatitis because the morphological characteristics of this skin disorder are similar.

Dermatologists ask standard questions to research subjects about the frequency of handwashing and the types of surfactants used during work. The identified surfactant content was then verified and categorized as a mild surfactant (ordinary household soap) and industrial surfactants (soaps containing scrubbing particles with or without solvent mixtures).

Personal skin exposure to cyclohexane solutes was measured with a dermal pad sampler for 3 consecutive days (Tuesday to Thursday). The pad sampler consists of 24 layers of surgical gauze cotton with a surface of 9 cm², worn on the volar forearm (wrist) for 8 working hours. The content of cyclohexane solutes in the pad sampler was determined using the NIOSH P & CAM 217 method and the plasma of all subjects was analyzed for the assessment of anti-NRL IgE by the immunosorbent assay enzyme.

Univariate logistic regression analysis was used to calculate the prevalence odds ratio (POR) through a comparison of certain skin conditions (for example, major and minor dermatitis) with subjects without skin symptoms. From 202 subjects, 14 workers were diagnosed with major hand dermatitis, 28% showed symptoms of minor hand dermatitis, and 17% were diagnosed with skin trauma (traumata). As many as 34.8% said their skin disorders were due to working conditions, and 41.6% said their skin disorders improved when they did not work for several days. The proportion of subjects claiming benefits after a few days off: 64.3% of those with major hand dermatitis, 42.9% with minor hand dermatitis, and 29.4% with traumata. Two subjects reported having an allergic reaction due to contact with rubber and chemical additives.

The relationship between frequency of handwashing with surfactant and minor hand dermatitis is further analyzed in stages according to the type of surfactant used. A clear dose-response relationship was found between the frequency of industrial surfactant use and the prevalence of minor dermatitis, the frequency of washing hands 5-9 times (167 workers) in all detergents, OR 3.09, 95% CI 1.16-8.21, industrial surfactants

(76 workers), OR 4.27, 95% CI 0.90-20.27, and mild surfactants (71 workers), OR 2.38, 95% CI 0.52-10.95, and frequency of hand washing 10 times (167 workers) in all detergents, OR 2.27, 95% CI 0.92-5.56, industrial surfactants (76 workers), OR 6.38, 95% CI 1.35-30.17, and light surfactants (71 workers), OR 1.17, 95% CI 0.28-4.80. For the aim of this report, only cyclohexanone and the outcome of irritant contact dermatitis are discussed in this report.

Discussion

The studies conducted by Febriana SA et al.⁸, Todd L et al.⁹, and Vermeulen R et al.¹⁰ investigate the effect of chemical exposure on the incidence of irritant contact dermatitis. The results from all three studies showed that the chemical, either alone or in a mixture of cyclohexanone with other chemical solvents, was equally responsible for the development of irritant contact dermatitis. The study design used in these three studies was cross-sectional. The quality of this study is still low and still needed stronger evidence because a cross-sectional only takes one measurement from data collection and no complete follow-up of the study patients, so it cannot be ascertained whether the cause occurred before the effect. In cross-sectional research, the measurement of variables is carried out at one point in time, prevalence data is obtained from this type of research. The relationship between prevalence in the exposed group and the unexposed group is called the prevalence ratio (PR). The best research design is a Randomized Controlled Trial (RCT), however, the cohort study can also provide scientific evidence stronger than a cross-sectional study because the study can establish the incidence, or the number of new cases of an outcome moving forward in time, within a certain population.

Subject characteristics between study groups in the Febriana SA et al.⁸ study, showed similar characteristics between departments, except for age and working hours/week. The second study conducted by Todd L et al.⁹ did not show the similarity characteristics between groups, almost all variables (age, employment, sex, smoking history, marital status, and educational background) were different between the five groups, including footwear factories (A, B, C, and D), and equipment factory. While the study conducted by Vermeulen R et al.¹⁰, almost all variables were different and also

not clearly defined for the age or employment. The similarity of subject characteristics is needed so the causal relationships that occurred were truly based on the individual subjects being studied.

Exposure and clinical outcome were measured in all three studies. The study result conducted by Febriana SA et al.⁸ showed that the highest exposure occurred in gluing and cleaning tasks. The factory has a continuous work process, without physical separation of the workplaces. Therefore, all workers were exposed to solvent vapors. Moreover, in the preparing/upper sole and assembling department, there were direct skin exposures to a wide variety of solvents and organic chemicals. The high prevalence of occupational contact dermatitis (9.5 %) in the assembling department may have been caused by heat exposure from heat-generating machines leading to a high ambient temperature (38–40°C) and humidity (80 %). It also described in other similar studies^{9,13,14} that the shoe manufacturing industry found that the workers' skin was exposed to methyl ethyl ketone, acetone, ethyl acetate, cyclohexane, and butyl acetate. In another study, it was explained that direct occupational exposure to solvents and detergents to the skin can cause occupational contact dermatitis. Cumulative irritants such as detergents or solvents require a repeated application to exert their noxious effects. The threshold for irritation varies from one individual to another, and a single individual may experience, over some time, hardening or loss of tolerance. However, with sufficient exposure and a high enough concentration of the irritant, everyone is prone to the development of ICD. Although itch is a frequent complaint, the main symptoms are pain or a burning sensation, and dermatitis presents as subacute to chronic eczema.¹⁵

The second study conducted by Todd L et al.⁹ found associations between chemical exposure hazards in footwear factories. Many of the chemicals and application methods were similar in the footwear and equipment factories, and the air concentrations were higher in the equipment factory. Some of the chemicals were found to spike up to six times from the occupational exposure limits. The equipment factory workers were observed to have significantly poorer work practices and housekeeping than any of the footwear factories. The reported prevalence of symptoms after being hired was much higher than the prevalence of symptoms before being hired for workers in both the footwear and equipment factories. This implies that

adverse health impacts were associated with working at the factories, and skin impairment such as dry or itchy skin, redness, and inflammation of hands or arms were significantly associated with chemical exposure. Some of the CNS depressants that were measured in the air included n-hexane, methyl ethyl ketone, toluene, xylene, ethyl acetate, cyclohexanone, and trichloroethylene. This is consistent with the findings that many of the VOCs found in footwear factories can irritate the eyes, skin, and respiratory system.

While a study conducted by Vermeulen R et al.¹⁰ showed that dermal exposure to cyclohexane-soluble agents at work was related to the occurrence of major hand dermatitis. Subjects with major hand dermatitis had erythema and papules with vesicles and sometimes fissures on the palms and the palmar sides of the fingers and fingertips. From the subjects with skin disorders, 34.8% attributed their adverse skin condition to working conditions encountered in the rubber manufacturing industry; 64.3% claimed relief of skin problems when not working for several days. Likewise as explained by Litchman G et al.¹⁶ that skin irritation caused by chemicals occurs due to sufficient inflammation arising from the release of proinflammatory cytokines from keratinocytes. It mainly causes disruption of the skin barrier, changes in epidermal cells, and the release of cytokines. Irritant contact dermatitis can present with three morphological patterns, acute phase: erythema, edema, oozing, crusting, tenderness, vesicles or pustules; subacute phase: crusting, scaling, and hyperpigmentation; and chronic phase: lichenification process occurs.

The lack of compliance in using chemical gloves of the worker, in this case, is similar to the Nuraga et al.¹⁷ explaining that it is necessary to protect workers from contact with chemical substances. Workers who always wear gloves properly will reduce the occurrence of contact dermatitis due to work both in quantity and duration course of contact dermatitis. The magnitude of the risk of a group of workers who sometimes use personal protective equipment (PPE) compared to the group of workers who use PPE against incidents of contact dermatitis (positive) was 8,556. This means that workers who sometimes use PPE have a risk of experiencing contact dermatitis 8,556 times greater than workers who always use PPE. The OR value (2,018 - 36,279) means that with a 95% confidence level, the respondent group sometimes uses PPE has a greater risk than the respondent group that always uses PPE. This is

because the minimum limit is greater than one (2,018 > 1) indicating a significant meaning that the group of respondents who sometimes use PPE tend to have a greater risk than the group of respondents who always use PPE for contact dermatitis (positive).

Dose-response gradient was not analyzed in those studies so was the dechallenge-rechallenge study. The dechallenge-rechallenge study is not possible to do in a cross-sectional study with a causal relationship between cyclohexanone exposure with the incidence of irritant contact dermatitis. The estimate's magnitude and precision regarding the association between the exposure and outcome in the study conducted by Febriana SA et al.⁸ cannot be assessed, the study only stated no statistically significant p-value in the prevalence of occupational skin dermatitis between departments, and the examination between departments. While a study conducted by Todd et al.⁹ showed that Prevalence Odds Ratio (POR) value > 1, shows a positive relationship between exposure and symptoms) and 95% CI value from the health questionnaire skin symptoms: dry or itchy skin on the hands or arms and redness on hands or arms, implies that there is a relationship between exposure to the symptoms. The third study conducted by Vermeulen R et al.¹⁰ showed that the relationship between 8 workers with high dermal exposure to cyclohexane and major hand dermatitis is OR 2.15 (95% CI 0.59-7.95) but this result was not significant statistically. However, the association makes biological sense that repeated exposure can damage skin structures, causing dryness, cracking, and dermatitis.¹⁸

Our patient is a woman, who worked as an operator in a shoe manufacturing company with complaints of redness and intermittent itching on the back of the right hand and left forearm. The complaint in the right hand occurs due to chemical exposure, the patient does not routinely use chemical gloves provided by the company because of heat and discomfort when used. Conditions were felt when returning to work, especially on Monday-Friday, and improved when the days off. The similarities between the patient and the articles were exposed to the irritant chemical and irritated the risk areas of the body (both hands), and it is similar to the third article that the complaints felt when returning to work and improved when the days off and the patient also have not complied to worn the protective gloves.

The number of articles obtained that met inclusion criteria were only three articles and the design of these studies was cross-sectional so it needs to be improved

because it was not shown sufficiently to be able to ensure that the exposure can lead to irritant contact dermatitis in workers. So more evidence is needed with a better study design to provide stronger evidence.

Conclusion and Recommendation

Conclusion

From three studies with a cross-sectional design, only one study shows a significant association statistically between solvent chemical mixture exposure including cyclohexane exposure on the incident of irritant contact dermatitis. The available evidence is not sufficient to ascertain that cyclohexanone exposure can lead to irritant contact dermatitis in workers.

Recommendation

For practice

Consider using tools to clean the logo screen printing so that workers are not in direct contact with the chemical, regular monitoring for workers with direct-cyclohexanone exposure and provide needed treatment, and they should wear appropriate protective gloves while working to avoid the incidence of occupational irritant contact dermatitis.

For research

Make research with a better study design to provide stronger evidence that cyclohexanone exposure can cause irritant contact dermatitis such as a cohort study that follows a group of individuals over time to assess the incidence of irritant contact dermatitis caused by cyclohexanone exposure, this study can be prospective or retrospective or a case-control/retrospective study in which a group of patients with irritant contact dermatitis (cases) is compared to a group of patients without the disease (controls). This case-control study aims to see whether exposure to any factor has occurred more or less frequently in the past in cases than in controls. Cases and controls may often be matched on basic demographic information (e.g. sex and age) to make the two groups as similar as possible.¹⁹

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