A study to characterise the “arsenic rash” observed at a copper smelter in Tsumeb, Namibia.

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Prepared by: Dr Greg Kew, Occupational Medicine Specialist

Supervisors: Prof Jonny Myers, Emeritus Professor of Occupational Health, UCT

Prof Gail Todd, Emeritus Professor of Dermatology, UCT

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DECLARATION

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1 ABSTRACT

This study is located at a copper smelter. Arsenic is a component of copper bearing ore and arsenic trioxide is a by-product of copper smelting. The vapours ("off-gases") that are released from the molten copper-bearing ore cool and condense in evaporative coolers to form arsenic-containing dust in the smelter's flues and stacks. The dust is filtered in "bag houses" and the captured powder is transported to Godfrey Roasters where the arsenic trioxide is driven off by heat. From there, the hot roaster gases are collected in what are known as "arsenic kitchens", where fume is allowed to cool. The arsenic trioxide settles to the floor of the rooms as coarse dust and also forms crystalline deposits on the walls and ceilings. It is removed from the kitchens and prepared for shipment as a dust containing approximately 98% arsenic trioxide. Workers are exposed to arsenic containing dust during maintenance work on the copper smelter's flues and the bag houses, or whilst performing various tasks in the arsenic plant roasters and kitchens. The smelter has approximately 500 permanent employees and variable numbers of contractors, which can increase the total employee compliment by 1000.

Skin rashes are the most common occupational disease reported at the copper smelter. The underlying cause of these acute transient rashes have historically been attributed by smelter employees to arsenic exposure, as encapsulated in the widely-used term, "arsenic rash".

Previous smelter reports have shown that the highest rates of skin rashes occurred at the arsenic plant and ausmelt baghouse. The appearance and anatomical distribution of the rash was described in these reports.

Notwithstanding the use of the term, "arsenic rash", the role of arsenic trioxide (As_2O_3) in the development of these rashes has been uncertain. In particular, a question has been raised as to whether the rash represents an allergy to either the arsenic trioxide or some other constituent of baghouse dust. Other uncertainties have related to the roles of skin hygiene practices and Personal Protective Equipment (PPE).

This study included three levels of enquiry: a detailed questionnaire (exploring personal risk factors, skin hygiene practices, PPE use and descriptions of the rashes experienced); a clinical examination by a dermatologist; and skin patch testing (using both standard allergens as well as selected chemical agents from 4 selected workplaces, namely "pure" As_2O_3 powder from the arsenic plant, baghouse dust from the ausmelt & convertor plants, and "cake" from the Effluent Treatment Plant ("ETP")).

Analysis of the chemical compounds present in the four samples was performed by an external certified laboratory in Pretoria, South Africa. For the purposes of skin patch testing, all four samples were "standardised" to 2g/dL As_2O_3 in water by the Smelter's quality assurance lab.

The epidemiological techniques varied according to the different objectives. For objectives 1 and 2: retrospective case control. For objective 3: exposure characterisation for use in exposure-response analysis. For objectives 4 & 5: retrospective case-control study, with controls matched for area of work in the smelter. Cases (N=27) comprised all employees who had one or more work-related rash incident within the preceding 12-24 months. These are relatively rare events, limiting the number of cases available for the study. Controls (N=24) comprised purposively selected co-workers, one control for each case, who performed the same type of work in the same workplace but who had never developed a rash.

The principal variables included potential determinants of skin reactions to workplace materials (pure arsenic dust from the arsenic plant, baghouse dust from the ausmelt and converter and filter cake from the effluent treatment plant), reactions to patch testing, a history of allergy, prior experience of a similar rash, duration of service in the smelter and age.

Ethical approval to conduct the study was obtained from the University of Cape Town's Health Research Ethics Committee (UCT HREC) (reference number 261/2016), and from the Office of the Permanent Secretary for Health, Namibia (letter dated 17 January 2018).

Five study objectives were formulated, the outcomes of which are summarised as follows:

Study objective 1: To interrogate if skin hygiene and hand cleansing practices used in the smelter, notably the use of barrier creams and soaps, are risk factors for developing a skin rash, and if so, at which anatomical location.

The study data showed that hand washing practices of cases and controls were very similar, suggesting that handwashing practices are not a risk factor for developing a skin rash at any anatomical location, notably the hands. Furthermore, the data showed that the hand cream being issued as a barrier to chemical contact is not protective.

However, both findings could be due to a non-differential bias whereby responses to the questionnaires in both groups of participants were influenced by a desire to appear compliant with company policy and conscientious with regard to cleanliness.

Study objective 2: To interrogate the use of PPE by employees in the smelter, and whether or not this is a contributory factor to the development of the rash

Whilst responses for the individual PPE related questions were generally similar in cases & controls, the combined prevalence of rashes in the area of the face (41%), respirator contact points (12.5%) and the neck area (19.6%) is high (73%). The rest of the body combined only accounts for 27%. Also, more specific questioning of the cases suggests that the respirators are a substantial contributor to the rashes in the face & neck areas. The lack of statistical significance between cases and controls for the individual PPE related questions could be due to the same non-differential bias operative in objective 1.

Study objective 3(a & b): To characterise the nature of the chemical constituents in the production by-products obtained from the various workplaces of the smelter operations ("workplace materials").

These "workplace materials" are the substances (usually in dust form) to which employees are exposed and which may trigger the skin reactions. The analysis addressed this in two ways; **objective 3a** looked at the chemical constituents of the workplace materials "as-is" (taken from the samples collected directly from the various workplaces as part of the smelter's Quality Assurance (QA) programme, and therefore as they are experienced by workers), and **objective 3b** looked at the chemical solutions used in the study skin tests, after standardisation for arsenic trioxide at 2g of arsenic trioxide per 100mL of water.

Objective 3a: The proportionate concentrations of As_2O_3 varied from 5% to 98% across the 4 samples from the 4 workplace locations, namely the arsenic plant (98%), ausmelt baghouse (83%), convertor baghouse (21%) and ETP (5%). Lead and sulphur were identified as additional potential irritants in the convertor baghouse dust and the ETP cake. Both baghouse dusts (ausmelt & converter) had alkaline pH, the As_2O_3 sample from the arsenic plant had an acid pH and the pH of the ETP sample was close to neutral.

Objective 3b: The samples were standardised to 2g/dL As_2O_3 in water, to better ascertain the skin responses to arsenic trioxide specifically at varying dilutions. This concentration was chosen because it is the point of solubility of arsenic trioxide in water. Consequently, the two samples with relatively lower As_2O_3 in the source material (converter Baghouse dust & ETP cake) had proportionately increased concentrations of their non-arsenic constituents after standardisation. These proportionate increases were 19% (ausmelt baghouse), 373% (converter baghouse) and 1799% (ETP). Should any of the non-arsenic constituents be irritants, their irritancies would be equivalently affected.

Following standardisation for arsenic, the pH for the ausmelt sample went up from pH 7.8 to pH 8.8, the converter sample went from pH 8.7 to pH 9.6 and the ETP sample went from pH 6.7 to 7.8. The arsenic plant sample had a pH of 4.5 after standardisation. Unfortunately, the smelter lab did not provide a pH of the pre-standardised arsenic plant sample. The high pH levels (8.8 & 9.6) or low pH level (4.5) are independently capable of causing irritation.

Study objective 4: To characterise the nature of the dermatological response to these exposures, notably whether the reactions are allergic or irritant in nature.

The main finding of this study is that arsenic trioxide is an irritant not an allergen, because of its low pH as well as an inherent dermal toxicity. The grounds for this conclusion are (1) the clinical appearance of the skin reactions where arsenic trioxide was in contact with the skin and (2) the dose-response relationship with increased concentrations of arsenic trioxide with the skin. The presence of arsenic trioxide in the baghouse dust and ETP cake confers irritant properties to these operational materials. The baghouse dusts are additionally irritant because of their high pH. The ETP cake produced a dose-dependent irritant reaction even though it was pH neutral.

Irritancy has implications on exposure prevention, in that all employees are potentially affected, not only a subset of vulnerable people.

Study objective 5: To try to ascertain any causal relationship between baghouse dust (and notably the As_2O_3 in the dust) and the pathological outcomes

The irritancy of arsenic trioxide in the arsenic plant sample was clearly demonstrable even though it was significantly diluted during the standardisation process (to 2g/dL). Arsenic plant workers in the real-world setting are exposed to undiluted concentrations of arsenic trioxide dust, which explains the high prevalence of irritant skin reactions amongst workers in this area.

This study has demonstrated that the alkaline pH of baghouse dust confers additional irritancy to that already conferred by the arsenic trioxide present in the dust. This explains the high prevalence of irritant skin reactions amongst workers exposed to baghouse dust.

This report ends with some recommendations, based on the findings of the study, as well as knowledge gaps identified.

2 INTRODUCTION

This study took place at a copper smelter located in Namibia, in Southern Africa. This smelter receives copper-containing ore concentrates from Eastern Europe and South America. Furnace fuel, ore concentrates, and additional materials are crushed and blended for introduction into a tandem sequence of two furnaces. The first is a "Top Submerged Lance" (TSL) or "Ausmelt" furnace fuelled by heavy furnace oil and oxygen. The second is a Peirce Smith furnace which converts the molten matte tapped off the Ausmelt furnace to blister copper (98.5%Cu). Both processes produce slag (molten silicate waste) and hot vapours "off gases". The off gases from the Ausmelt pass through evaporative coolers and are then filtered through a baghouse where the arsenic containing dust is captured and transferred to an arsenic plant where it is further processed to produce arsenic trioxide. The filtered gas containing sulphur dioxide is transferred to a sulphuric acid plant gas cleaning system where it is further processed to produce sulphuric acid.

Workers are exposed to arsenic containing dust during maintenance work on the copper smelter's flues and the bag houses, or whilst performing various tasks in the arsenic plant roasters and kitchens. The smelter has approximately 500 permanent employees and variable numbers of contractors, which can increase the total employee compliment by 1000.

Employees often report to the occupational health staff at the smelter with skin rashes. The underlying cause of the rash has historically been attributed by smelter employees to arsenic exposure, as encapsulated in the widely-used term, "arsenic rash".

A mid-2017 review[1] of cases who presented to the on-site occupational health staff revealed that cases happened most often during certain maintenance tasks, such as during shut-downs, and lacked seasonality. The highest numbers occurred at the arsenic plant and ausmelt baghouse. The common feature of these two sites is the "baghouse dust", which is both a by-product of the smelting process, and the feedstock for the arsenic plant. The anatomical distribution of the rash seemed to be mostly in the face & neck area. Features regarded as risk factors for experiencing a rash included wearing a respirator, poor personal hygiene, not shaving, poor workplace supervision and inadequate training.

The clinical features attributed to the rash by the occupational health staff varied from mild to severe. In early cases of a reaction the affected area is warm, itchy, red and slightly swollen, which with ongoing exposure develops maculo-papular lesions, which may break down with some weeping of serous fluid. With progressive exposure, the papules become more extensive and blister, with breakdown and weeping, until in severe cases, the skin reaction becomes wide-spread with weeping & crusting. In relapsing cases, the skin becomes thickened and pigmented.

In 2014, a case of "arsenic rash" at the smelter was referred to the South African National Institute of Occupational Health in Johannesburg for further investigation[2]. Patch testing (using samples of baghouse dust and arsenic trioxide) plus a clinical examination by a dermatologist showed that it was irritant contact dermatitis[2]. Reactions to baghouse dust followed a gradient proportional to the concentration of the dust, whereas there was no skin reaction to "pure" arsenic trioxide. The baghouse dust was found to have a pH of 10, which is corrosive to the skin. Other constituents of the dust included: Cu 2.3%, Pb 2.4%, As 52.7%, Fe 2.3%, CaO 6.8%, S 2.3%. (data from smelter lab – test 9208; 30-10-2014)

Given this background, this study aimed to better characterise the skin rash and explore associations with the arsenic (arsenic trioxide) and baghouse dust. In addition, given its arsenic content, the "cake" from the effluent treatment plant was also included. The study also looked at other factors that may impact the incidence of rashes, such as the use of Personal Protective Equipment (PPE).

[1] Skin rashes – a review of cases over the period 2014-2017 (as of May 2017). Report for Smelter management by Dr Greg Kew.
[2] Investigation conducted on cause of skin rash on a Smelter employee, National Institute of Occupational Health, Johannesburg. Dec 2014

3 LITERATURE REVIEW

This study examines the adverse *dermal* effects of dust containing arsenic trioxide in *direct contact* with the skin of employees of a *copper smelter*. Hence this literature review prioritised papers involving *direct dermal contact* with *inorganic arsenic compounds* in *occupational* settings. Noting that the workers participating in this study also had high systemic levels of arsenic, the literature review included papers featuring key *dermatological features* of chronic arsenic absorption.

3.1 Background

Arsenic is a ubiquitous metalloid present in ground water, soil, and air, and is also found in food supplies. Arsenic is found in inorganic and organic forms and it is generally the inorganic compounds that are the toxic ones. Some species of marine plants such as algae and seaweed, and marine organisms such as crustaceans and some fish, often naturally contain high concentrations of organic arsenic.[46] The World Health Organization (WHO) has listed arsenic as one of its ten chemicals of major public concern.[49] Inorganic arsenic is listed as the number one concern on the priority list of hazardous substances by the Agency for Toxic Substances and Disease Registry (ATSDR). [42,43] The International Agency for Research on Cancer (IARC) has listed arsenic as a skin carcinogen. [53]

Man-made sources of arsenic are most commonly by-products of smelting non-ferrous metal ores, primarily copper and to a lesser extent lead, zinc & gold. Other industrial sources include the manufacture of arsenic containing insecticides, wood preservatives, semiconductors, glass and lead-acid batteries.[42, 46]

3.2 Brief chemistry of arsenic compounds of relevance to occupational dermatology

Arsenic compounds can be classified as *inorganic* arsenic and *organic* arsenic.

Inorganic arsenic compounds contain arsenic (As) and at least one other element, but no carbon. Inorganic arsenic exists in four main chemical forms known as valency or oxidation states. Valency is a measure of the ability of a compound to combine with other elements, such as hydrogen. The dominant forms are *arsenite*, with a valency of 3, also referred to as trivalent arsenic (As (III), As+3), and *arsenate*, with a valency of 5, also referred to as pentavalent arsenic (As (V), As+5. [41, 42, 44, 46] Examples of inorganic arsenic include arsenic trioxide, arsenic pentoxide, and sodium arsenate.

Organic arsenic compounds are those containing carbon. They are mainly found in sea-living organisms, although some of these compounds have also been found in species living on land. [42, 45, 46] Examples of organic arsenic include arsenobetaine & arsenocholine (in fish), cacodylic acid and sodium methylarsenate acid (in pesticides).

The water solubility of the arsenates and arsenites depends on the metal to which they are bound. The alkali-metal arsenites (eg. sodium arsenite) are freely soluble in water, the alkaline-earth arsenites (eg calcium arsenite) are slightly soluble, and the heavy-metal arsenites are insoluble (eg. copper arsenite). [46]

Under conditions of smelting, most of the arsenic occurs as an oxide, most of it being in the trivalent and not the pentavalent form. [12] The compound of arsenic produced in largest quantity is arsenic trioxide and the largest use of arsenic is in the production of agricultural pesticides, desiccants, wood preservatives and agricultural feed additives. [42, 46] Arsenic is added to poultry feed for the purposes of inducing faster weight gain on less feed, and creating the perceived appearance of a healthy colour in meat from chickens, turkeys and hogs.

Arsenic trioxide is an inorganic compound with the formula As_2O_3. It is poorly soluble in water (1.2g/100ml at 0°C, 2.1g/100ml at 25°C, and 5.6g/100ml at 75°C). The rate of dissolution in water is very low, and several weeks are required to achieve equilibrium. [46]

3.3 Copper smelting and arsenic trioxide

Arsenic is a component of copper bearing ore and arsenic trioxide is a by-product of copper smelting. The vapours ("off-gases") that are released from the molten copper-bearing ore cool and condense in evaporative coolers to form arsenic-containing dust in the smelter's flues and stacks. The dust is filtered in "bag houses" and the captured powder is transported to Godfrey Roasters where the arsenic trioxide is driven off by heat. From there, the hot roaster gases are collected in what are known as "arsenic kitchens", where fume is allowed to cool. The arsenic trioxide settles to the floor of the rooms as coarse dust and also forms crystalline deposits on the walls and ceilings. It is removed from the kitchens and prepared for shipment as a dust containing approximately 98% arsenic trioxide. [12]

Workers are exposed to arsenic containing dust at various places throughout the smelter, but particularly high exposures occur during maintenance work on the copper smelter's flues and the bag houses, or whilst performing various tasks in the arsenic plant roasters and kitchens.

Arsenic trioxide is mainly absorbed from inhaled dust via the lungs and swallowed dust in the gastrointestinal tract. [12] No quantitative studies were located on absorption of inorganic arsenicals in humans after dermal exposure. Experiments on rats (Dutkiewicz)[6] and Rhesus monkeys (Lowney)[9] have shown that arsenic in aqueous solutions can penetrate through intact skin, albeit in low rates in the order of 2.0-6.4% of the applied dose.

3.4 Adverse dermal health effects of skin contact with arsenic

The adverse health effects of arsenic on humans have been extensively researched, but the majority of publications address community exposure to ingested arsenic in groundwater and food supplies. There is relatively little written on occupational arsenic exposure, and in particular on the dermal effects of direct skin contact with arsenic.

The causticity and skin irritancy of arsenic trioxide, particularly in creases where clothing binds, have been long recognised as the primary symptom in smelter workers or their families exposed to dusts with a high arsenic content. [1, 5, 10, 12, 14] A striking consequence of direct contact with mucous membranes of the nose is perforation of the nasal septum, sometimes occurring after only a week or two of exposure. [4, 15] It was these caustic properties that, in the 19th century, led to arsenic being used as a "cancer paste" - it was used to remove skin tumours. [6]

Dunlap (1921) [4] suggested that inhaled particles of *arsenic trioxide* can collect on the nasal septum where the dust dissolves on the moist mucous membrane. Should high concentrations develop, this could result in localised ulceration, damaged blood supply and erosions of the underlying cartilage of 3-8mm in diameter.

Downing (1934)[2] reported on cases of chronic arsenic poisoning from various medications being prescribed at the time, notably Fowler's solution. Downing's clinical findings in these cases included dermatitis with keratoses, wheals, papules, excoriated vesicles and pigmentation.

Holmqvist (1951) [7] studied workers in a large copper-ore smelting facility over a 2-year period and concluded that most of their skin eruptions (either vesiculation or folliculitis) were based on contact allergy. He noted that, on patch testing, 80% of arsenic workers (ie. previously sensitised) reacted to concentrations of *sodium arsenite*, *sodium arsenate*, and *arsenic pentoxide* that caused reactions in

only 35% of non-arsenic workers and 30% of new employees. Note that all three of these compounds are highly soluble in water, whereas arsenic trioxide is not. [42, 44, 45]

Pinto and McGill (1953)[12] described *arsenic trioxide* exposure at large copper smelters in Denver, Colorado and Tacoma, Washington. They observed that contact irritant dermatitis was the most common lesion. Because arsenic containing dust tended to irritate the skin where the respirator rested on the face, they lined the employees' respirators with surgical wadding over the nose and cheeks. Notably, they found no cases of hyperpigmentation nor keratosis, and noted that clinical evidence of systemic toxicity was rarely detected in their settings of occupationally inhaled arsenic, even though many employees had more than 30 years of employment.

Birmingham et al (1964) [1] reported clinical findings of an outbreak of arsenical dermatoses in a mining community. They found a variety of skin and mucous membrane lesions including a pruritic contact dermatitis, folliculitis, pyoderma, ulcerations, conjunctivitis and rhinitis. The dermatitis usually involved the face and flexures. Perforation of the nasal septum was observed only in the arsenic roaster operators. On the basis of a patch test (using 5% arsenic in starch) the authors concluded that allergy was not an important factor.

In a patch test study of dermal sensitization for *sodium arsenate* and *sodium arsenite* by Wahlberg and Boman in 1986 [14], only 2 of 379 cases tested (0.5%) were positive. The few positive responses seemed to be due to a cross-reactivity with nickel. Their studies in guinea pigs did not yield evidence of a sensitization reaction to inorganic arsenic.

Gonçalo (1989) [5] described occupational contact irritant dermatitis to *arsenic trioxide* in three men in the glass industry. The lesions included pruritic maculopapules, pustules and folliculitis mainly localised in exposed and moist areas. Symptoms were worse in summer. Patch tests with the pure workplace chemicals gave a pustular and follicular reaction to arsenic trioxide in two patients. When applied in dilutions of 5%, 2% and 1% in petrolatum, reactions were negative - as well as in 25 controls. The authors found peripheral neuropathy in all three cases, without any other systemic findings.

In 1998, Mohamed [10] evaluated 11 male workers at a tin smelting factory where *arsenic trioxide* levels ranged from 5.2 to 14.4 mg/m^3. The workers experienced symptoms of generalized itch, dry and hyperpigmented skin, folliculitis, and superficial ulcerations. The authors concluded that arsenic-containing dust collected on the sweat on the workers' skin, causing contact irritant dermatitis.

3.5 Brief review of the adverse skin health effects of systemic absorption of ingested arsenic

The medicinal use of arsenic, although practised for hundreds of years, apparently reached a peak in the middle to late 1800's and was a mainstay in the limited medical armamentarium of the time. [6] "Fowler's solution", a remedy popularised by an English physician in the late 18th Century, Dr Thomas Fowler, contained 10g of arsenic trioxide per litre of water (1% arsenic trioxide), in combination with potassium bicarbonate (20g) and compound tincture of lavender (30ml). It was used to treat various ailments, including syphilis, psoriasis, acne, diarrhoea, gastric ulcer, asthma, malaria, lupus, psoriasis, neurodermatitis, eczema, rheumatism. [2, 6] Therefore, many patients received arsenic for months and years. It was in such patients that the consequences of long term administration of arsenic were first recognised to be palmar and plantar hyperkeratosis, characteristic pigmentary changes on the trunk, and a variety of cancerous and precancerous lesions on the hands, feet, and trunk. [2, 6]

In **Southwestern Taiwan** in the **1920's**, due to the high salinity in shallow groundwater in this area, residents began using artesian wells as a water source. In this geographic location, groundwater naturally contaminated with arsenic was widespread. Following the adoption of this source of drinking

water, a peripheral vascular disease known as “Blackfoot Disease” became endemic in the area. Epidemiological studies also showed increased rates of various cancers, including skin cancer. [11, 40]

In **Northern Chile**, in **1957**, arsenic containing river water was diverted to provide drinking water to over 250 000 people, resulting in excessive exposure over a 13-year period. Studies showed high rates of various cancers and increased mortality rates. [11, 37]

Whilst exposure to arsenic in the water supplies in Taiwan and Chile are largely historical, in **Bangladesh** and **India** (especially West Bengal) the exposure to arsenic in drinking water is ongoing.

Fifty districts of Bangladesh and 9 districts in West Bengal, India have arsenic levels in groundwater above the World Health Organization's maximum permissible limit of 50 µg/L. The area and population of 50 districts of Bangladesh and 9 districts in West Bengal are 118,849 km2 and 104.9 million and 38,865 km2 and 42.7 million, respectively.[30, 31] Arsenic exposure in these communities has been extensively researched and cases of arsenicosis have been reported since the 1980’s. [24, 26, 29, 33]

In **Bangladesh**, the high arsenic containing water was not discovered until the 1990’s when an epidemic of skin lesions emerged (see further description of these skin lesions below). The Health Effects of Arsenic Longitudinal Study (HEALS) was established in 2000 by a group of investigators at Columbia University to evaluate the effects of the full range of arsenic concentrations on various health outcomes. [16, 19].

In **Pakistan**, a cross-sectional survey in 2012 of skin lesions of arsenicosis from groundwater in Khairpur, Pakistan found an overall prevalence of arsenicosis skin lesions of 13.5 %. The prevalence of skin lesions increased with increased levels of arsenic in drinking water. [21]

The results of a survey of chronic arsenic poisoning in drinking water in **Inner Mongolia** published in 2007 revealed that over 400 000 people are at risk from arsenic poisoning in that region. Clinical and epidemiological investigations were carried out on 13 021 people to ascertain the nature and degree of morbidity that occurred due to chronic arsenic toxicity. In all of the studied patients, 22% had typical hyperkeratosis on the palms or soles and some had raindrop-like hyperpigmentation and depigmentation on the trunk. [22]

The skin lesions of chronic ingestion of arsenic comprise collection of unique skin changes, known as *arsenical keratosis* (or *arsenicosis*). [16-40]

Arsenical keratosis typically starts with hyperpigmentation (melanosis) followed by keratotic skin nodules. The keratoses are usually multiple and typically occur at sites of friction and trauma, especially on the palms and the soles. They usually manifest as small, punctate, nontender, horny, hard, yellowish, often symmetric, corn-like papules. The diameter of the papule ranges from 0.2-1 cm. Sudden increases in the size of the size of the keratotic lesions suggest malignant transformation. The skin carcinomas associated with chronic arsenic ingestion include Bowen’s disease, squamous cell carcinoma, and basal cell carcinoma.

A mild form of the arsenical keratoses may manifest as diffuse thickening or small (< 2 mm) keratoses with sandpaper–like texture. Moderate-sized lesions (2-5 mm) may coalesce into larger (>5 mm) verrucous papules or plaques. These lesions are most frequently seen on the thenar and lateral borders of the palms; the base and lateral aspect of the digits; the soles, heels, and toes of the feet, as demonstrated in the image below. Keratoses may also develop on the dorsum of the hands, the arms, and the legs.

The melanosis can be diffuse or patchy, or exhibit a distinctive symmetrically distributed pattern of fine macules in a “raindrop” pattern, these lesions often appearing on the trunk of the body. Leucomelanosis

(white and black markings) also occurs, but less frequently than melanosis or keratosis. Mee's lines, which are white bands traversing the nail bed, are seen in chronic arsenic exposure.

A dose-response relationship exists between the amount of arsenic exposure and the frequency of various skin lesions.

Whilst several studies have shown skin lesions that have developed in persons exposed to arsenic at concentrations of less than 50 µg/L ([Ahsan et al [16], Haque et al [24], Rahman et al [30,31], Roychowdhury [33]), a detailed investigation by Smith et al [37], who accounted more carefully for long term exposure, found that the characteristic skin lesions required arsenic exposures in drinking water of greater than 100-200µg/L, and an average latency of 23 years since first exposure. [38]

Hall, et al, compared drinking water, urinary arsenic (UAs) and blood arsenic and the risk of skin lesions. They found that at levels of UAs 36-64, 65-113, 114-201 and 202-1230 µg/L of arsenic was associated with adjusted rate ratios for skin lesions of 1.63 (95% CI 0.92-2.89), 1.73 (0.99-3.02), 2.00 (1.13-3.56) and 3.16 (1.73-5.76). Rate ratios were adjusted for age, gender, BMI, and smoking status. [23]

The US Environmental Protection Agency (EPA) calculated the Lowest Observable Adverse Effect Level (LOAEL) for skin effects from chronic arsenic ingestion, in mg/kg/day, to be in the order of 1.4×10^{-2} to 2.2×10^{-2}. [20]

Apart from the skin, the long term toxic effects of high levels of absorbed arsenic include a broad range of organs and systems, including the nervous system, respiratory system, cardiovascular system, liver, kidney, bladder, immune system, endocrine system and also certain developmental processes. [16-40, 42]

4 STUDY OVERVIEW

The study participants comprised 27 cases & 23 controls, making a total of 50. The inclusion criteria are described in the procedure section below.

Each study participant signed consent, underwent a structured interview, a skin examination by a dermatologist, and finally had skin patch testing. These patch tests comprised a standard battery of workplace allergens (see appendix 2), plus dilutions of dust taken from the workplace (arsenic plant, converter baghouse, ausmelt baghouse and effluent treatment plant filter "cake").

The study was initially considered to require two phases; the first being a retrospective review of cases of employees who had previously experienced a rash, and the second being a prospective case by case assessment of employees as they present with their rashes. This 2-phased approach was thought necessary to meet the study objectives, as there was uncertainty as to whether sufficient information would be obtained from the retrospective data.

However, the information obtained from phase 1 has met all the study objectives, rendering phase 2 unnecessary. Nonetheless, this report will make recommendations for ongoing case management. The researchers intend to use the learning from this study to develop a standardised protocol (questionnaire, examination, and photographs that the smelter team may use going forward, from which they may expand the understanding of the clinical evolution of these cases). The information derived from the new protocol will be subjected to annual analysis & reporting.

The protocol for this study was approved by the ethics committee of the Health Sciences Faculty of the University of Cape Town.

5 OBJECTIVES

1. To interrogate the skin hygiene and hand cleaning practices used in the smelter, notably the use of barrier creams and soaps.
2. To interrogate the use of PPE by employees in the smelter, and whether or not this is a contributory factor to the development of the rash.
3. To characterise the nature of the chemical constituents in the production by-products obtained from the various workplaces within the smelter operations ("workplace materials"), notably the baghouse dust, cake in the effluent treatment plant ("ETP"), and arsenic trioxide from the arsenic plant.
4. To characterise the nature of the dermatological response to these exposures, notably
    - Whether the reaction is irritant or allergic.
    - Whether atopy is a risk factor.
5. To try to ascertain if there is a causal relationship between baghouse dust (notably the arsenic in the dust) and the pathological outcomes.

6 METHODS

6.1 Study type

The epidemiological design varied according to the different objectives. For objectives 1 and 2: retrospective case control. For objective 3: exposure characterisation for use in exposure-response analysis. For objectives 4 & 5: retrospective case-control study, with controls matched for area of work in the smelter.

6.2 Variables measured

The principal variables included potential determinants of skin reactions including workplace dust (pure arsenic dust from the arsenic plant, baghouse dust from the converter and ausmelt), filter cake from the effluent treatment plant), reactions to patch testing, a history of allergy, prior experience of a similar rash, duration of service in the smelter and age.

Variables that might be independent determinants of skin reactions include components of the baghouse dust (including low or high alkalinity), weather conditions, type of work, use and nature of PPE and skin hygiene practices.

Potential confounding or effect modifying variables of the relationship between arsenic and skin reactions include atopy or other dermatoses (skin conditions) such as psoriasis, seborrheic dermatitis, rosacea and acneiform reactions.

6.3 Measurement techniques

Measurements of constituents of workplace production by-products of plant operations

- Four samples of workplace materials in the form of arsenic trioxide dust from the (1) arsenic plant, baghouse dust from the (2) converter & (3) ausmelt, and filter cake from the (4) effluent treatment plant were collected by smelter staff. These samples are routinely collected for quality control checking at the on-site laboratory.

- These workplace materials were selected because an analysis of skin rash cases[3] showed that a high proportion of skin rashes were circumstantially attributed to exposure to these workplace materials in the arsenic plant and baghouses.
- The arsenic content of the workplace materials was measured using inductively coupled plasma mass spectrometry (ICP-MS) by the on-site laboratory, to enable subsequent standardisation for arsenic trioxide content in the samples used for skin testing.
- The chemical constituents of the workplace materials were measured using ICP-MS by a certified laboratory, Chemtek Laboratory Services.

Standardisation of arsenic trioxide content across the four test samples used for patch testing

A key objective of the study was to ascertain the effects of arsenic trioxide on the skin. However, the workplace materials to be tested were obtained from four different workplaces. The results of patch tests using these four workplace samples could only be made comparable by ensuring the arsenic contents of each were the same.

To achieve this, the proportionate contents of As_2O_3 of each workplace sample were measured by a certified toxicology laboratory. The results are shown in Table 12. The arsenic content across the 4 samples varied from 5% to 98%.

To remove this confounding effect of variable arsenic trioxide content, the samples were standardised to 2.1g/dL As_2O_3 in water, as this is the solubility of arsenic trioxide in water at room temperature [46].

To achieve 2.1g/dL of arsenic trioxide in each test sample, the appropriate quantities of each workplace sample were placed in distilled water as follows:

- Arsenic Plant materials: (98.31% arsenic trioxide): 2.07g in 100ml distilled water.
- Ausmelt Baghouse materials: (82.91% arsenic trioxide): 2.53g in 100ml distilled water
- Converter Baghouse materials: (20.78% arsenic trioxide): 10.11g in 100ml distilled water
- ETP materials: (5.20% arsenic trioxide): 40.38g in 100ml distilled water

These standardised samples were prepared at least a week prior to patch testing, to allow for the slow dissolution of arsenic trioxide in water. They were called the “neat” samples when it came to patch testing. On each day of patch testing, these neat samples were further diluted in distilled water to 1:10, 1:100 and 1:1000.

The impact of this standardisation on the non-arsenic trioxide constituents, including irritants, is that they will have increased in the samples from the Ausmelt, Convertor and ETP by 0.19x, 3.73x and 17.9x respectively.

Clinical assessments

Participants recruited into the study were asked to:

- answer questions posed in a structured **questionnaire (see appendix 2)**
- be **examined** clinically by the dermatologist

[3] Skin rashes – a review of cases over the period 2014-2017 (as of May 2017). Report for Smelter management by Dr Greg Kew.

- be **patch tested** using standard allergens and dilutions of workplace dust (from the different workplaces where they worked) (see appendix 3 & appendix 4)

6.4 Selection of participants

Participant inclusion criteria were as follows:

- The **case group** (N=27) comprised all employees who had presented to the on-site occupational health unit for one or more work-related rash incident within the preceding 12-24 months. These are relatively rare events, limiting the number of cases available for the study.
- The **control group** (N=24) comprised purposively selected co-workers, one control for each case, who performed the same type of work in the same workplace but who had never developed a rash.

On the basis of the above, a list of prospective participants was compiled.

On the day of testing, each person on the list was invited to participate in the study by staff members of the smelter's occupational health centre; those who agreed were required to sign a consent form. Only one employee, a control, declined the offer to participate.

Cases and controls then proceeded to administration of the questionnaire, then to clinical examination by the dermatologist, then finally to patch testing.

Questionnaires (see appendix 2)

The day prior to testing, the researcher spent time with selected staff members of the occupational health centre, training them how to administer the questionnaire.

The questionnaire comprised sections addressing:

- Information sharing and consent (see appendix 1)
- Basic socio-demographic data such as occupation, age and sex
- Medical history
- Workplace skin management & hygiene practices, use of Personal Protective Equipment (PPE)
- Workplace factors
- For those who had rashes at work, features of the rash (timing, onset, appearance, etc)

Patch Testing

Patch testing included three phases:

1. Preparation of test materials (chemical substances to be tested) NB: see section 6.3, under Methods, for details on how these test materials were prepared, and also standardised to contain 2g/dL of arsenic in each sample.
2. Application of the test solutions
3. Interpretation of the outcomes

This process is described in detail in the appendix 5.

7 ETHICAL APPROVAL

Ethical approval to conduct the study was obtained from the University of Cape Town's Health Research Ethics Committee (UCT HREC) (reference number 261/2016) (see Appendix 7), and from the Office of the Permanent Secretary for Health, Namibia (letter dated 17 January 2018)(see Appendix 8). The purpose and objectives of the study were explained to each participant who was provided with a written description forming part of the informed consent form. Potential subjects were told that they were free to refuse participation or withdraw from the study at any time. Subjects' identities were protected by a numerical coding system and the questionnaires and data were kept securely locked away and subject to computer password protection.

Potential Benefits

The results of the study will make a valuable contribution to the understanding of the relationship between workplace exposures and skin reactions that are reported at copper smelters worldwide. There are few studies on this topic, and those that exist are old; yet the problem is seemingly commonly encountered at smelters. This improved understanding will lead to improved control measures and reduced morbidity.

Potential risks

Participants were made aware that the research process included skin patch testing which may cause irritant or allergic skin reactions to the allergens, but these are expected to be relatively mild and short-lived.

8 RESULTS

8.1 Participant characteristics

Table 1: Sex distribution

	Male		Female		Totals	
Cases	24	89%	3	11%	27	53%
Controls	20	83%	4	17%	24	47%

Table 2: Average age and years of service

	Average Age	Average years of service
Cases	35.1 years	4.6
Controls	41.9 years	5.6

8.2 Questionnaires

(A copy of the questionnaire is in appendix 2

Medical Background

Table 3: Prevalences of participants with a background of non-work-related symptoms of all allergies

	Number of participants with non-work-related allergic symptoms	Percentage	Number of allergies diagnosed by a doctor	Percentage
Cases	7/26	27%	3/27	11%
Controls	7/23	30%	3/24	13%

This table shows that there was no meaningful difference between cases and controls for answers to questions about the presence of pre-existing allergies.

Table 4: Prevalences of participants with a history of doctor-diagnosed non-work-related symptoms of skin allergies

	Number with background of **eczema**	Percentage	Number with background of **urticaria**	Percentage
Cases	0/27	0%	4/27	15%
Controls	2/24	8%	0/24	0%
		p=0.216*		p=0.169*

* Fisher's Exact Test of significance.

This table shows that, for pre-existing skin allergies, controls had a higher prevalence of eczema whilst cases had a higher prevalence of urticaria. However, neither of these differences was statistically significant.

Table 5: Prevalences of participants with a history of self-reported allergies to metals

	Number who have rashes when exposed to non-work-related metals (buttons, jewellery)	Percentage
Cases	7/25	28%
Controls	2/24	8%
		p=0.065*

* Fisher's Exact Test of significance.

The above table shows that prevalences of rashes when exposed to metals were >3x higher in the case group.

Prevalences were similar for the two groups for dry skin, itchiness when sweating, acne, greasy skin and rashes when exposed to sunlight.

Workplace skin management & hygiene practices

Table 6: Responses to questions relating to workplace skin management & hygiene practices

	Cases	Controls
Hand washing at work	25/27=93%	22/23=96%
Average number of times hands washed in a workday	4.5	5.3
Use of soap	27/27=100%	22/23=96%
Wash before going to the toilet	20/25=80%	19/23=83%
Use of protective hand cream	10/27=37%	6/23=26% p=0.173*

* Fisher's Exact Test of significance.

Responses were similar in both groups, except for the more frequent use of protective hand cream reported by cases.

PPE use

Table 7: Responses to questions relating to PPE use

	Cases Numbers/% (hours)	Controls Numbers/% (hours)
Head gear / helmet	24/27=89 (6.6)	19/23=83 (6.8)
Overalls	25/27=93 (7.1)	20/23=87 (7.4)
Protective glasses	23/25=92 (6.6)	18/19=95 (6.8)

	Cases Numbers/% (hours)	Controls Numbers/% (hours)
Gloves	22/27=81 (5.2)	20/22=91 (6.8)
Boots / shoes	25/27=93 (7.2)	21/23=91 (6.8)
Mutton cloth*	7/9=78 (6.1)	8/8=100 (6.8)
Mask*	3/3=100 (8.3)	4/5=80 (6.8)
Respirator	24/27=89 (6.7)	18/22=82 (6.8)
Full body suit*	10/11=91 (4.0)	12/14=86 (6.8)

Although there were some minor differences, responses were generally similar in both groups.

* Note: The 3 questions with poor responses related to the use of “mutton cloth”, masks and full body suits. Poor responses to “mutton cloth” were probably because the use of mutton cloth is discouraged by management, as it interferes with the protective function of respirators. The poor responses to “mask” use were probably because the term is ambiguous, and the respondents were unclear if the question related to “respirators” or something else. On review, this question should not have been included. The poor responses to “full body suit” use is not clear. However, these suits are only used by workers in the arsenic plant whilst doing maintenance work in the kitchens, so it is likely that many of the respondents were entirely unfamiliar with the term and therefore did not respond.

This note is also included under “Limitations”.

Factors related to the occurrence of skin rashes (cases only) (N=27)

Table 8: Circumstances in which skin rashes occurred (cases only)

Hot vs cold Responses = 23/27		Rainy vs dry Responses = 14/27		Windy vs still Responses = 13/27	
Hot	Cold	Rainy	Dry	Windy	Still
21	1	1	12	7	6

Note: The responses for Table 8 were based on the subjects’ abilities to remember weather conditions, which very few could remember. No response means the individual could not remember. The low response rates of the rainy/dry and windy/still questions, as well as the reliance on memory for this type of information reduce the interpretability of these answers

The weather conditions most predisposing to rashes appear to be hot & dry. Windiness appears not to play a determining role.

Note: The responses for Tables 9, 10 & 11 were derived from a list of items for each question, from which the subject was asked to choose, by marking the applicable box with an “x”. See Questionnaire; questions 24, 25 & 27). Therefore, only positive responses are recorded; negative responses were not required.

Table 9: PPE items that employees view as contributory to their rashes (cases only)

	Helmet	Overalls	Goggles	Gloves	Boots	Mutton Cloth	Respirator	Full suit
"yes" responses	1	1	0	2	0	2	4	1
% of yes responses	9.1%	9.1%	0.0%	18.2%	0.0%	18.2%	36.4%	9.1%

Whilst the numbers are small, for cases it seems the respirator is most commonly linked to the rashes.

Table 10: Anatomical distribution of the skin rashes (cases only)

Respirator contact	Nose	Around eyes	Rest of face	Neck	Forearms	Hands	Groins	Back	Chest	Legs
7	6	5	12	11	2	3	1	2	2	2
12.5%	10.7%	8.9%	21.4%	19.6%	3.6%	5.4%	1.8%	3.6%	3.6%	3.6%

The denominator here is 56, being the number of responses to the options available in the questionnaire. There is a relatively high proportion of rashes in the area of the face (41%) and respirator contact (12.5%) and the neck area (19.6%). The rest of the body combined only accounts for 27%.

Table 11: Appearance of the skin rashes as per selections made by cases from questionnaire options

	Redness	Colour change	Pain	Itchy	Wet	Palpable	Burning	Dry	Scaly
No of yes responses	11	13	11	22	10	26	11	8	8
% of the 27 cases	40.7%	48.1%	40.7%	81.5%	37.0%	96.3%	40.7%	29.6%	29.6%

This pattern of symptoms is in keeping with the symptoms described by the on-site clinic staff, described in the Introduction.

They are in keeping with an irritant reaction, as one would see with a mild chemical "burn".

8.3 Workplace test materials

The Table below shows the constituents of the dust samples (% composition by mass), taken from the workplace locations as per the samples used for patch testing. These were tested by SANAS accredited Chemtek Laboratory Services in November 2019.

Table 12: Constituents of the workplace materials prior to standardisation for patch testing*

Substance	Arsenic Plant % Total	Ausmelt Baghouse % Total	Converter Baghouse % Total	ETP % Total
Arsenic Trioxide	98.3122	82.9097	20.7815	5.1978
Aluminium	<0.0004	0.1517	0.2130	0.0474
Bismuth	0.0941	0.9546	2.9580	2.4727
Calcium	0.0175	3.2379	1.3522	8.8935
Cadmium	0.2224	0.3165	0.3828	0.1404
Copper	0.0207	1.4292	2.2753	7.8998
Iron	0.0130	1.5658	0.5293	0.4922
Potassium	<0.0004	0.4645	0.1310	0.0077
Magnesium	<0.0004	0.1225	0.1140	0.2563
Phosphorous	<0.0004	0.0229	0.1398	0.0841
Lead	0.1193	4.5645	17.3351	12.3631
Sulphur	<0.0004	2.1426	10.3539	8.7690
Antimony	0.8453	0.7948	0.7006	0.3337
Selenium	<0.0004	0.0303	0.1493	0.0341
Tin	0.0124	0.2776	0.8726	0.8179
Tellurium	0.0193	0.1868	0.2587	0.1136
Zinc	0.0181	1.3928	4.2217	1.2378

*Source: Chemtek Laboratory Services lab report 08/11/2020 (reference CLS192849).

Note. These were not the exact samples used for patch testing, but from the same workplace locations as the samples used for patch testing. See Limitations section.

Table 13: Proportional content of arsenic trioxide in each sample & impact of standardisation

	Arsenic Plant Total Conc (%)	Ausmelt Baghouse Total Conc (%)	Converter Baghouse Total Conc (%)	ETP Total Conc (%)
As_2O_3	98.3122%	82.9097%	20.7815%	5.1978%
Standardisation effect** ->	-	0.19	3.73	17.9

** The "standardisation effect" is the effect on the relative concentrations of substances in each sample, after they have been adjusted to 2g/dL As_2O_3 in water. The values in Table 13 represent the relative changes in concentration of the non-arsenic constituents after the samples are standardised for arsenic trioxide (diluted to get the As_2O_3 the same for all samples). The implication of this is the non-As_2O_3 constituents, including irritants, in the matching columns in the table above will have been relatively increased by these factors. Hence the non-arsenic constituents of the samples from the Ausmelt, Convertor and ETP will have increased by 0.19x, 3.73x and 17.9x respectively.

Table below shows the pH values for the samples, as measured by smelter laboratory and also by the research team prior to patch testing.

Table 14: Measured pH for each sample

	Arsenic Plant	Ausmelt Baghouse	Converter Baghouse	ETP
pH measured by smelter lab pre standardisation	- (Not available)	7.8 (Sample 34424)	8.7 (Sample 34428)	6.7 (Sample 34432)
pH of neat samples measured by smelter Lab post standardisation	- (Not available)	8.81 (Sample 34424)	9.56 (Sample 34428)	7.8 (Sample 34432)
pH of neat samples measured by the research team during study (litmus paper)	4.5	8.5	- (Litmus test failed)*	7.0

* The litmus strip was unreadable (went black from the particles in suspension).

Summary of above results

Results prior to standardisation: The proportionate contents of As_2O_3 varied from 5% to 98% across the 4 samples. Lead and sulphur were identified as additional potential irritants in the converter baghouse dust and the ETP cake. Both baghouse dusts (ausmelt & converter) had alkaline pH, the As_2O_3 sample from the arsenic plant had an acid pH (4.5) and the pH of the ETP sample was close to neutral (6.7).

Results after standardisation: To remove this confounding effect of variable arsenic trioxide content, the samples were standardised to 2.1g/dL As_2O_3 in water. The consequence of this is that the two workplace samples with relatively lower As_2O_3 in the source material (converter Baghouse dust & ETP cake) had proportionately increased concentrations of their combined non-arsenic constituents after standardisation. These proportionate increases were 19% (ausmelt baghouse), 373% (converter baghouse) and 1799% (ETP). Should any of the other constituents be irritants, their irritancies would be equivalently affected.

The pH for the baghouse dusts went up slightly (pH 8.8 & 9.6) as did the pH of the ETP cake (pH 7.8). The “pure" As_2O_3 in the arsenic plant had a pH of 4.5. These pH levels (high or low) are independently capable of causing irritation.

8.4 Results of skin patch testing – smelter workplace materials

The nature of the skin reactions to smelter workplace materials

All the reactions to workplace materials were “irritant” in nature and none were classified as “allergic” by the Dermatologist in the research team. They follow a typical dose-dependent response rate, with maximal reactions to “neat” solutions, and minimal reactions to highly dilute solutions. Reactions were felt by participants within 12-24 hours but disappeared by 48-72 hours. The borders demarcating contact / no contact with the test samples were clearly defined. Irritant reactions are based on direct damage to the skin cells by the chemical, leading to a local inflammatory response. These features contrast with the features of contact allergy, where the reactions are delayed (typically by 48-72 hours, or even up to 96 hours). Allergic reactions spread beyond the borders demarcating contact / no contact with the test samples. (see section below, describing "Results of skin patch testing – standard allergens”.)

The skin reactions comprised varying degrees of epidermal injury confined to the area of contact with the chemical. The visually observed effects (only observable under magnification) included inflammatory reactions affecting various skin elements, in particular the hair follicles. These reactions included colour changes (pink to red); inflammatory vesicles, some of which developed pustular content, and sometimes cellular breakdown.

Figure 1: Photographs of progressive reactions to workplace materials

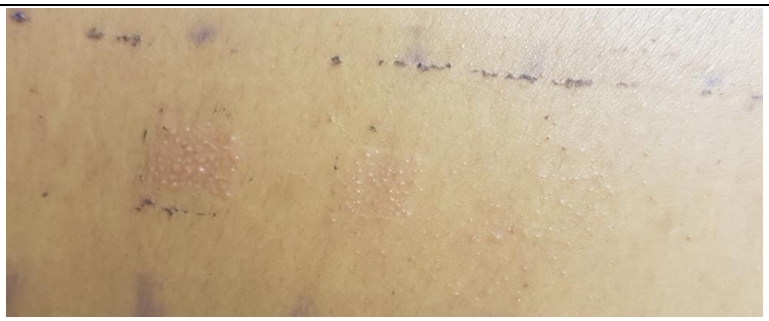
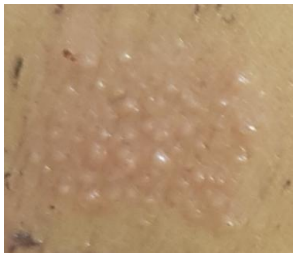
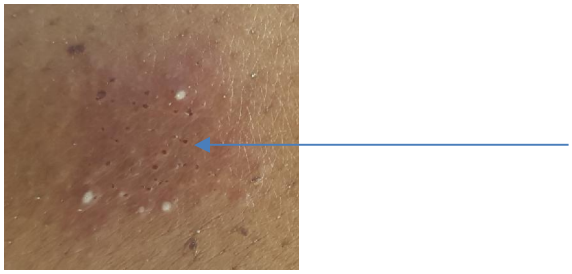
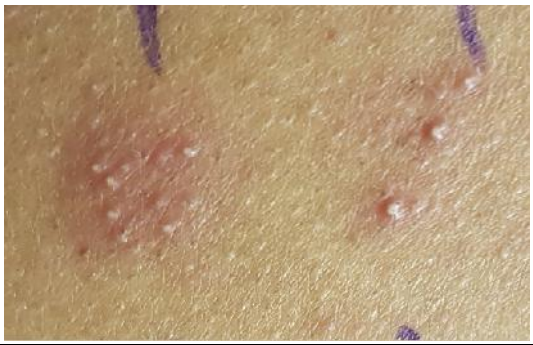
	This photograph demonstrates the progression of acute irritant skin reaction (left = “neat”, with increasing dilutions (decreasing concentrations) to the right). Note the discreetly demarcated areas of colour change and papules.
	This photograph also demonstrates the progression of acute irritant skin reaction (left = “neat”, with increasing dilutions (decreasing concentrations) to the right). Note the “edge effect” where the edge of the test chamber presses on the skin and occludes follicles, leading to small pus containing inflammatory vesicles.

Figure 2: Photographs of reactions to workplace substances at high magnification

	This image demonstrates the early inflammatory effects of contact between the skin and the workplace material, including a papular reaction with a pinkish colour change.
	This image demonstrates a more reactive response, in which the papules have developed pus-containing vesicles and the redness is more marked. Note the small the brownish discolouration at the tips of some of the papular reactions representing cellular damage to the epidermis.

	This image demonstrates more clearly a reaction in which the papules have developed pus-containing vesicles, surrounded by redness.

These findings of redness (starting with faint follicular spots, up to dusky red areas with haemorrhages), vesicles (blisters), pustules, and erosions are typical features of an acute irritant reaction, as described by Frosch, et al [50].

Comparisons of prevalences of reaction by type of material

Important notes to these comparisons

- The arsenic content in each of the workplace test samples has been **standardised** to a neat value of 2g/100ml. This means that the *arsenic* content in the prepared neat solutions for As_2O_3, ausmelt baghouse dust, converter baghouse dust and ETP cake are the same, as are their subsequent dilutions. The advantage of this is that it removes the effect of varying concentrations of arsenic in the "raw" 4 workplace material samples. Any differences in reactivity in the standardised solutions must therefore be caused by something other than arsenic.

  Given that the percentages of arsenic in the primary (unprepared) samples are converter 20.8%, ausmelt 82.9%, ETP 5.2% and As_2O_3 98.3% (see Table 2), the effects of standardisation to the same quantity of arsenic will be to dilute them according to their arsenic concentration ($As_2O_3$was diluted most, and the ETP diluted least).

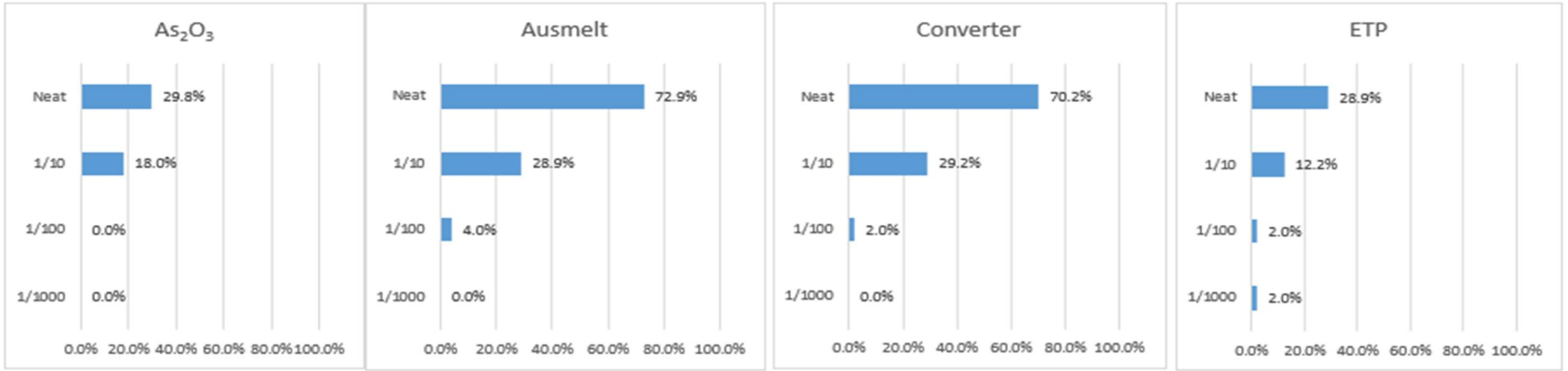
- The workplace material called "As_2O_3" is the arsenic trioxide produced by the arsenic plant; it is not the baghouse feedstock entering into the arsenic plant. It was used in this study to represent "pure" arsenic, although the actual percentage is 98%.

- The reaction prevalences expressed in this section are the prevalences for the standardised workplace materials in the patch tests; they do not represent prevalences of reactions in the workplaces by the same names (ie ausmelt, converter, ETP).

Table 15: Patch test results for workplace materials at varying dilutions – **cases & controls combined**

PATCH TEST RESULTS	As Plant	As Plant	As Plant	As Plant	Ausmelt	Ausmelt	Ausmelt	Ausmelt	Converter	Converter	Converter	Converter	ETP	ETP	ETP	ETP
	46	47	48	49	51	52	53	54	61	62	63	64	56	57	58	59
	As_2O_3	As_2O_3	As_2O_3	As_2O_3	Ausmelt	Ausmelt	Ausmelt	Ausmelt	Converter	Converter	Converter	Converter	ETP	ETP	ETP	ETP
	1/1000	1/100	1/10	Neat	1/1000	1/100	1/10	Neat	1/1000	1/100	1/10	Neat	1/1000	1/100	1/10	Neat
CASES + CONTROLS	Note: 1 control was classified "invalid".															
Category	1/1000	1/100	1/10	Neat	1/1000	1/100	1/10	Neat	1/1000	1/100	1/10	Neat	1/1000	1/100	1/10	Neat
No Positive	0	0	9	14	0	2	13	35	0	1	14	33	1	1	6	13
No Negative	50	49	41	33	50	48	32	13	50	48	34	14	49	49	43	32
Out of	50	49	50	47	50	50	45	48	50	49	48	47	50	50	49	45
% Positive	0.0%	0.0%	18.0%	29.8%	0.0%	4.0%	28.9%	72.9%	0.0%	2.0%	29.2%	70.2%	2.0%	2.0%	12.2%	28.9%
Fisher's exact test (neat vs 1/10)			p= 0.130				p< 0.001				p< 0.001				p= 0.040	
Fisher's exact test (1/10 vs 1/100)			p= 0.001				p= 0.001				p< 0.001				p= 0.053	

Figure 3: Graphs of patch test results for workplace materials at varying dilutions – cases plus controls combined



pH: arsenic plant: 4.5 % As before dilution: 98.3% = most diluted	pH ausmelt: 8.81 % As before dilution: 82.9% = 2nd most diluted	pH converter: 9.56 % As before dilution: 20.8% = 2nd least diluted	pH ETP 7.8 % As before dilution: 5.2% = least diluted

Summary of the above results.

1. The “neat” arsenic concentration is standardised at 2g/dL of arsenic trioxide for all 4 workplace samples.
2. The overall irritancy after standardisation for arsenic trioxide was **ausmelt baghouse dust > converter baghouse dust > ETP cake**. The irritancy of the As_2O_3dust was approximately equal to the ETP cake.
3. The reaction prevalences for all 4 workplace test materials show a graduated response from neat to 1/10, and from 1/10 to 1/100. This is particularly more evident in the ausmelt and converter samples.
4. The concentration-dependent irritancy of pure arsenic trioxide is evident. The irritancy could be because of its moderately low pH (4.5) or because of some other inherent chemical toxicity.
5. Comparison between the arsenic plant and the ETP samples.
   a. The irritancy of neat arsenic trioxide was similar to the irritancy of neat ETP. The irritancy of ETP cannot be explained by its pH, being near neutral (7.8).
   b. As both samples had similar concentrations of arsenic, and pH could not explain the irritancy of ETP, this suggests that the *arsenic* was the cause for the irritancy in both samples.
   c. If any non-arsenic component(s) in the ETP sample had contributed to the irritancy, their combined irritancy would have made ETP more irritant than the pure arsenic sample. As the irritancy of the neat arsenic trioxide was similar to the irritancy of neat ETP, this means the non-arsenic components did not contribute to irritancy. Note that the non-arsenic components of the ETP sample were minimally diluted.
   d. For both samples, the irritancy diminished with increasing dilution. However, the ETP still had some irritancy at higher dilutions (1/100 & 1/1000).
6. Comparison between the arsenic plant sample and ausmelt sample.
   a. Even though the standardisation dilutions were similar for the arsenic plant and ausmelt samples, the irritancy of the ausmelt sample was higher. The main difference between the two was the pH (the ausmelt was strongly alkaline, whereas the arsenic plant was moderately acidic).
7. Comparison between the ausmelt sample & converter sample:
   a. Even though the standardisation dilution was much higher for the ausmelt sample than the converter sample, its irritancy was similar. The main similarities between the two were their similarly high pH and their standardised arsenic content.
   b. The combination of the highly alkaline pH plus the arsenic content of the two baghouse samples will have contributed to their high levels of irritancy.
8. Combining the findings above:
   a. The irritancy of the arsenic plant sample is explained, in part at least, by its pH (acidity), but this does not exclude a contribution from an inherent chemical toxicity to the skin.
   b. The comparison between the arsenic plant and ETP samples showed that the ETP sample’s irritancy was independent of pH, and had no contribution from its non-arsenic component. Hence the ETP sample’s irritancy must be solely due to the arsenic content.

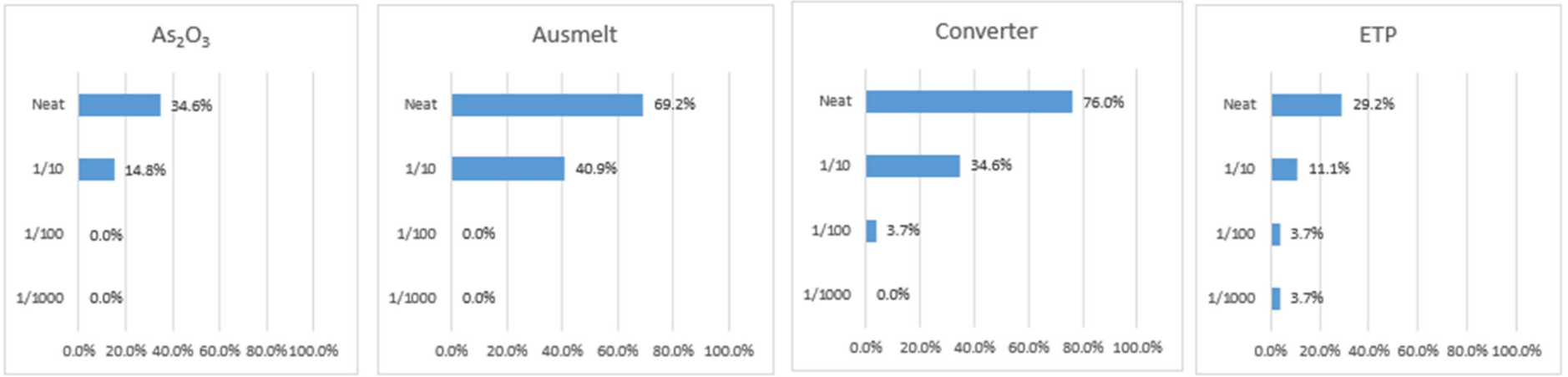
c. Points 8.a & 8.b suggest that the irritancy of arsenic trioxide is contributed by a low pH (demonstrated by the sample in its pure form) as well as an inherent toxicity to the skin, independent of pH (demonstrated by the arsenic in the ETP sample). The relative contributions of these two characteristics to the irritancy of arsenic trioxide cannot be conclusively ascertained from this study.
d. The relatively high irritancy of the baghouse samples compared to the ETP and arsenic plant samples is explained by the pH (alkalinity) of their total constituents combined with the inherent irritancy of their arsenic content.

9. Whilst Table 12 (results section on workplace materials analysis) shows significant proportions of lead and sulphur, known skin irritants, the comparative analysis of the arsenic plant and ETP samples (5 above) indicate that the non-arsenic components of the samples contributed minimally to irritancy.

Table 16: Patch test results for workplace materials at varying dilutions – **cases only**

PATCH TEST RESULTS	As Plant	As Plant	As Plant	As Plant	Ausmelt	Ausmelt	Ausmelt	Ausmelt	Converter	Converter	Converter	Converter	ETP	ETP	ETP	ETP
	46	47	48	49	51	52	53	54	61	62	63	64	56	57	58	59
	As_2O_3	As_2O_3	As_2O_3	As_2O_3	Ausmelt	Ausmelt	Ausmelt	Ausmelt	Converter	Converter	Converter	Converter	ETP	ETP	ETP	ETP
	1/1000	1/100	1/10	Neat	1/1000	1/100	1/10	Neat	1/1000	1/100	1/10	Neat	1/1000	1/100	1/10	Neat
CASES ONLY																
Category	1/1000	1/100	1/10	Neat	1/1000	1/100	1/10	Neat	1/1000	1/100	1/10	Neat	1/1000	1/100	1/10	Neat
No Positive	0	0	4	9	0	0	9	18	0	1	9	19	1	1	3	7
No Negative	27	26	23	17	27	27	13	8	27	26	17	6	26	26	24	17
Out of	27	26	27	26	27	27	22	26	27	27	26	25	27	27	27	24
% Positive	0.0%	0.0%	14.8%	34.6%	0.0%	0.0%	40.9%	69.2%	0.0%	3.7%	34.6%	76.0%	3.7%	3.7%	11.1%	29.2%
Fisher's exact test (neat vs 1/10)			p= 0.087				p= 0.046				p= 0.015				p= 0.102	
Fisher's exact test (1/10 vs 1/100)			p= 0.060				p< 0.001				p= 0.005				p= 0.305	

Figure 4: Graphs of patch test results for workplace materials at varying dilutions – cases only



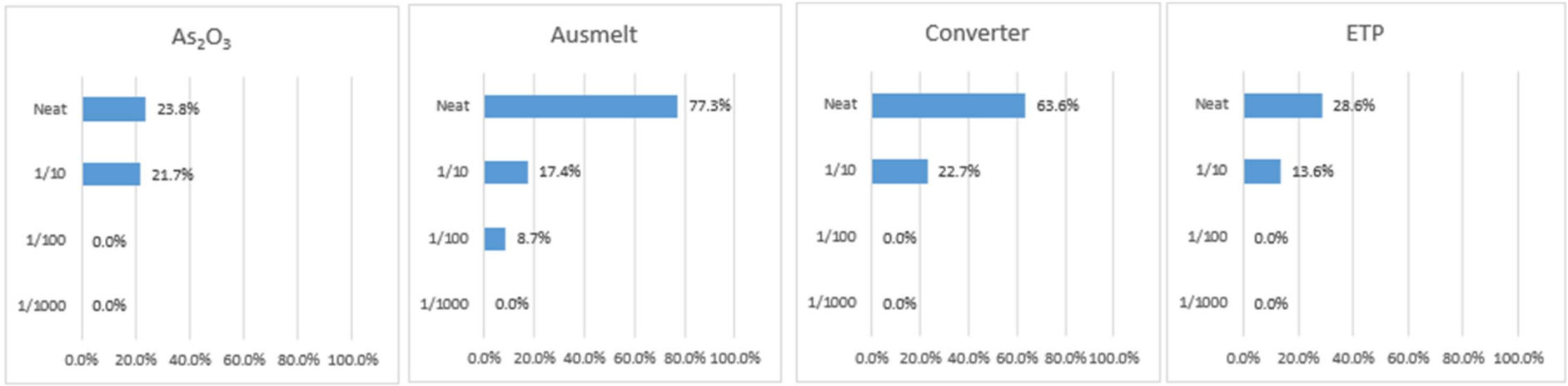
Comment

The reaction prevalences in the case group are similar to the combined group. Note that the graduated response rate from neat to 1/10 and from 1/10 to 1/100 is very significant for ausmelt and converter, and close to significant for the arsenic plant sample.

Table 17: Patch test results for workplace materials at varying dilutions – **controls only**

PATCH TEST RESULTS	As Plant	As Plant	As Plant	As Plant	Ausmelt	Ausmelt	Ausmelt	Ausmelt	Converter	Converter	Converter	Converter	ETP	ETP	ETP	ETP
	46	47	48	49	51	52	53	54	61	62	63	64	56	57	58	59
	As_2O_3	As_2O_3	As_2O_3	As_2O_3	Ausmelt	Ausmelt	Ausmelt	Ausmelt	Converter	Converter	Converter	Converter	ETP	ETP	ETP	ETP
	1/1000	1/100	1/10	Neat	1/1000	1/100	1/10	Neat	1/1000	1/100	1/10	Neat	1/1000	1/100	1/10	Neat
CONTROLS ONLY	Note: 1 control was classified "invalid".															
Category	1/1000	1/100	1/10	Neat	1/1000	1/100	1/10	Neat	1/1000	1/100	1/10	Neat	1/1000	1/100	1/10	Neat
No Positive	0	0	5	5	0	2	4	17	0	0	5	14	0	0	3	6
No Negative	23	23	18	16	23	21	19	5	23	22	17	8	23	23	19	15
Out of	23	23	23	21	23	23	23	22	23	22	22	22	23	23	22	21
% Positive	0.0%	0.0%	21.7%	23.8%	0.0%	8.7%	17.4%	77.3%	0.0%	0.0%	22.7%	63.6%	0.0%	0.0%	13.6%	28.6%
Fisher's exact test (neat vs 1/10)			p= 0.576				p< 0.001				p= 0.007				p= 0.204	
Fisher's exact test (1/10 vs 1/100)			p= 0.025				p= 0.333				p= 0.024				p= 0.109	

Figure 5: graphs of patch test results for workplace materials at varying dilutions – controls only



Comment

The reaction prevalences in the control group are also similar to the combined group. A noticeable difference is that there is a big step down in response rates from neat to 1/10 for the ausmelt and converter samples, whereas for arsenic trioxide the difference in minimal. It is noteworthy that this group represents employees who have never experienced a rash at work, yet they have similar looking rates of reaction to the workplace materials, under controlled experimental conditions, to those who have experienced rashes at work. This similarity is tested for significance in the following table.

Table 18: Comparison of reactivity of cases and controls

Fisher's exact test (cases vs controls)	As_2O_3: Neat				Ausmelt: Neat				Convertor: Neat				ETP: Neat			
	Cases	Controls	Total		Cases	Controls	Total		Cases	Controls	Total		Cases	Controls	Total	
No Positive	9	5	14		18	17	35		19	14	33		7	6	13	
No Negative	17	16	33	p value	8	5	13	p value	6	8	14	p value	17	15	32	p value
Total	26	21	47	0.316	26	22	48	0.385	25	22	47	0.272	24	21	45	0.613

Fisher's exact test (cases vs controls)	As_2O_3: 1/10				Ausmelt: 1/10				Convertor: 1/10				ETP: 1/10			
	Cases	Controls	Total		Cases	Controls	Total		Cases	Controls	Total		Cases	Controls	Total	
No Positive	4	5	9		9	4	13		9	5	14		3	3	6	
No Negative	23	18	41	p value	13	19	32	p value	17	17	34	p value	24	19	43	p value
Total	27	23	50	0.394	22	23	45	0.079	26	22	48	0.281	27	22	49	0.562

Ausmelt: 1/100				Convertor: 1/100				ETP: 1/100			
Cases	Controls	Total		Cases	Controls	Total		Cases	Controls	Total	
0	2	2		1	0	1		1	0	1	
27	21	48	p value	26	22	48	p value	26	23	49	p value
27	23	50	0.207	27	22	49	0.551	27	23	50	0.540

ETP: 1/1000			
Cases	Controls	Total	
1	0	1	
26	23	49	p value
27	23	50	0.540

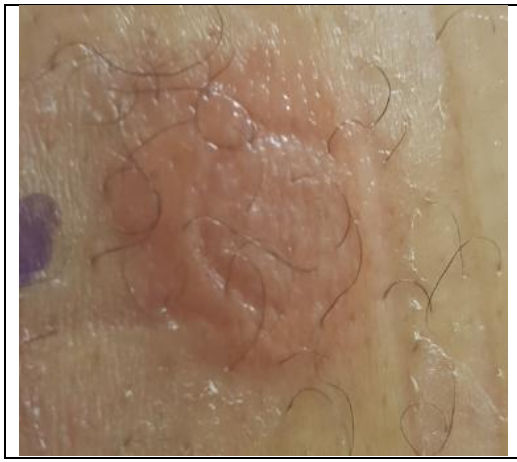
Comment

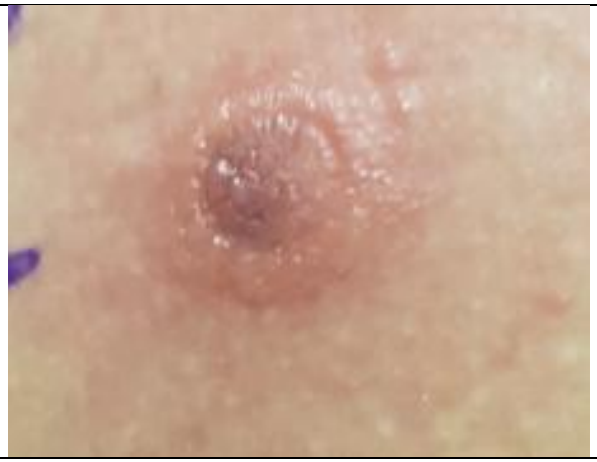
This table shows a series of 2x2 tables in which the reactivity rates of cases and controls are compared, at neat concentrations and the sequential dilutions (1/10, 1/100 and 1/1000). Note that for dilutions at which neither cases nor controls had any reactions, the Fisher's exact test is not applicable. None of the "p-values" are below 0.05, meaning that there is no statistical difference between cases and controls for all four test materials, and at all dilutions.

8.5 **Results of skin patch testing – standard allergens**

Allergic skin reactions are different to irritant reactions in several ways. They take longer to evolve (typically only seen after 48 or 72 hours) and take longer to recover. The reaction is disproportionate to the level of exposure and extends beyond the contact area with the allergen. The underlying mechanism is an immunological response to the chemical as opposed to a chemical "burn".

Figure 6: Examples of allergic reactions to standard allergens





Note how the reaction extends beyond the contact area with the alleren. The area is swollen and red. Thereare no papules and no folliculitis.

Table 19: Outcomes of patch tests for standard allergens

Allergens	Irritant	Allergic		
		+	++	+++
Carba Mix	1	1	0	0
Clioquinol	0	0	1	0
Cobalt Chloride	0	0	1	0
Colophony	0	0	1	0
Fragrance Mix	1	1	3	0

Explanatory note:

Irritant reactions are simply scored 1 for "irritant" or 0 if not.

Allergic reactions are given a "severity" score: (+ - +++)

+ = weak reaction, non-vesicular, erythema, infiltrated

++ = strong reaction, vesicular plus papules

Allergens	Irritant	Allergic		
		+	++	+++
Fragrance Mix II 14%	0	1	0	0
Kathon CG/CI + Me-isothiazolinone	1	0	0	0
Lyral	0	1	0	0
Nickel Sulphate	0	0	6	0
Paraphenylenediamine	0	0	0	1
Potassium Dichromate	0	1	0	0
p-Tert-butylphenol formalin	0	1	0	0
Thiomersal	0	1	0	1
Thiuram Mix	0	0	1	0
Wood Tar Mix	2	4	3	0

+++ = extreme (bullous)

This table illustrates the frequencies of irritant & allergic reactions for the standard allergens listed; it shows the most frequent allergic reactions were for wood tar mix, then nickel then fragrances. Note also that some of the allergens also produced irritant as well as allergic reactions. (For a description of how allergy is distinguished from irritancy, see earlier section "The nature of the skin reactions to smelter workplace materials")

Table 20: Distribution of reactions – cases versus controls

	No of positive reactions to allergens	% Positive reactions to allergens (N=25)
Cases	15	60%
Controls	10	40%

Comments:

The proportion of reactions to standard allergens (not work related) is slightly higher in the case group, but this difference is not statistically significant (Fisher's exact test (p = 0.28)). This lack of significance could be due to the small sample size.

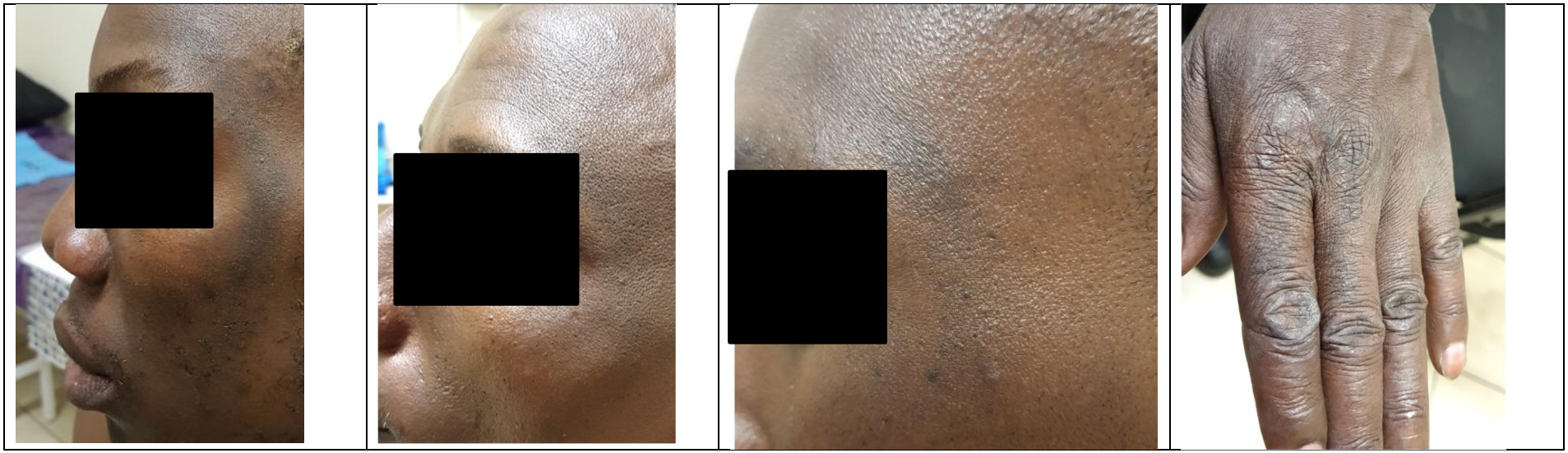
7 cases and 1 control reacted to more than one allergen.

8.6 Features worth mentioning from the skin examinations

This section will describe some of the dermatological features of interest that were encountered in the course of examining participants.

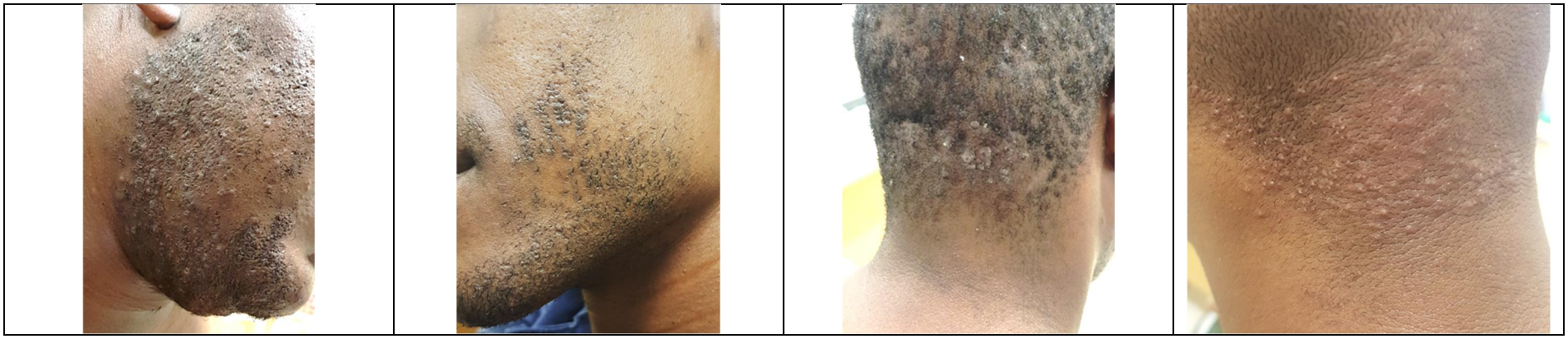
In unstructured conversation during the clinical examinations, it became apparent that PPE, in particular respiratory protective equipment (RPE), plays a contributory role in the various skin related issues. The constant use of a respirator causes discomfort in the contact zones, resulting in irritation & itching. Repeated episodes lead to increased pigmentation (first 3 images below). The 4th image below shows increased pigmentation and skin thickening from repeated irritation caused by glove use.

Figure 7: Issues related to PPE – contact & occlusion



The smelter generally prohibits facial hair for employees who are required to wear a respirator. This principle is widely adopted at workplaces worldwide and is based on the understanding that facial hair prevents the formation of a secure seal between the respirator and the skin, thereby adversely impacting the effectiveness of the respirator. The problem is that these respirators are worn for extended periods (on average over 6 hours per day according to the interviews conducted in this study), and the combined effects of sweat, irritant dust and occlusion of the skin all conspire to cause significant discomfort.
To comply with the facial hair prohibition, employees must shave. Some employees develop skin complications from shaving, such as demonstrated in the images below. Various factors increase the risk of these complications, such as occlusion of the skin and the use of razor blades that are sub optimally sharp.

Figure 8: Issues related to PPE – shaving & occlusion



These adverse effects are likely to adversely impact compliance with use of a respirator. To this end, the smelter has instituted a relaxation of the close-shave policy, allowing for a short hair growth.

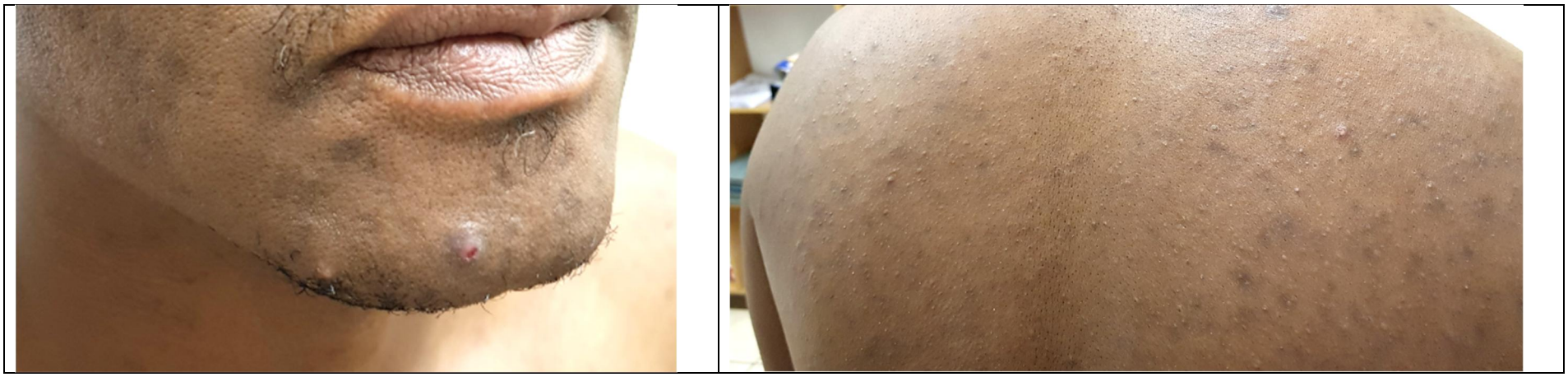
Smelter employees have long made use of an informal solution to this problem of contact irritation – a piece of mutton cloth draped around the face, between the skin and the respirator. See image below.

Figure 9: Mutton cloth used to perevent facial skin problems

This seems to ameliorate the problem but comes at the potential cost of adversely impacting the effectiveness of the respirator. It is unclear as to which impacts more on the effectiveness of the respirator; the non-compliance caused by the discomfort at the respirator contact zone or the use of mutton cloth. This could not be answered in this study, as only 9 cases and 8 controls reported using mutton cloth.

Another skin problem commonly encountered during the clinical examinations was acne – on the face, back and chest. The causes of acne are multifactorial but constant occlusion is a significant risk factor.

Figure 10: Acne on the face and back



9 DISCUSSION

General findings

The main aims of the study were to interrogate the skin hygiene, hand cleaning practices and PPE use in the smelter to ascertain if these may be linked to development of the rashes, and to characterise the nature of the dermatological response to exposures to workplace materials, notably whether the reaction is irritant or allergic.

The main finding is that arsenic trioxide is an irritant not an allergen, because of its low pH as well as an inherent dermal toxicity. The presence of arsenic trioxide in the baghouse dust and ETP cake confers irritancy to these operational materials. The baghouse dusts are additionally irritant because of their high pH.

The results showed no statistical difference between cases and controls for skin hygiene, hand cleaning practices and PPE use. Whilst the data did not demonstrate statistical significance due to small numbers, it suggests that individuals with contact allergy have more reactive skin and that this would predispose them to more severe irritant rashes.

In Tables 1 & 2, the gender distribution shows a male dominance, which correctly reflects the gender distribution of workers at this workplace. The controls are slightly older than the cases with a slightly higher average length of service. This may reflect a mild “survivor” effect (employees who develop rashes may tend to leave the smelter to seek employment elsewhere).

Table 5 shows that prevalences of reportedly allergic rashes when non-occupationally exposed to metals were >3x higher in the case group. This difference is not statistically significant, probably because of small numbers of subjects, but nevertheless suggestive of individual hypersensitivity among cases.

Interestingly, even though the participants were drawn from occupations of high exposure to arsenic, four of whom have been employed for over 10 years, none of them displayed the classic skin features of arsenicosis. On average, they have been employed for 4-5 years. The absence of arsenicosis in this group may be because, as noted in the literature review, according to a detailed investigation by Smith et al [37], the characteristic skin lesions require arsenic exposures in drinking water of greater than 100-200µg/L, and an average latency of 23 years since first exposure. [38]

Study objective 1: To interrogate the skin hygiene and hand cleaning practices used in the smelter, notably the use of barrier creams and soaps.

A limitation of this study was that this type of information was dependent on accurate answers given by the study participants - there was no realistic opportunity to fully interrogate the veracity of the answers given. From the study data it is apparent that employees wash their hands extensively (4-5 times in a workday), both before and after using the toilet. Both groups reported low use of protective hand creams.

Two interesting findings emerged from this data.

- The hand washing practices of cases and controls were very similar, suggesting that handwashing practices are not a risk factor for developing a skin rash.
- The cases used the protective cream more (37% versus 26%). This difference was not statistically significantly different which is suggestive that the hand cream is not protective.

However, both findings could be due to non-differential bias, whereby employee responses in both groups of participants were influenced by a desire to appear compliant with company policy and conscientious with regard to cleanliness.

Study objective 2: To interrogate the use of PPE by employees in the smelter, and whether or not this is a contributory factor to the development of the rash

The responses were generally similar in cases & controls, the differences for all the individual PPE related questions being statistically non-significant. This suggests that specific PPE use (category or duration of use) does not appear to be a contributory factor to the development of the rash. This objective is similarly reliant on

accurate responses from participants as for objective 1, so the non-differential bias caused by the desire to appear compliant with company standards is likely to be operative in these findings too.

However, for cases, the combined prevalence of rashes in the area of the face (41%), respirator contact points (12.5%) and the neck area (19.6%) is high (73%). The rest of the body combined only accounts for 27%. (Table 10). Furthermore, a large proportion of cases (36%) indicated that they viewed the respirator as a cause for the rashes. (Table 12). The responses to the more in-depth enquiry with the cases are more likely to represent the true situation. Also, the link between irritancy and the contact points of respirators corresponds with the findings of the smelter's own analysis (mentioned in the introduction).

One would expect the respirator contact zone to experience a high prevalence of skin reactions because of occlusion, abrasion from dust particles in suspension and sweat collection. The "rest of face" experiences high rates of skin reaction because it is most directly exposed to airborne dust. The neck is also area of contact with the respirator strapping and also where sweat collects.

Study objective 3: To characterise the nature of the substances in the workplace materials (notably the baghouse dust and filter cake in the effluent treatment plant ("ETP").

The analysis addressed this in two ways; **objective 3a** looked at the workplace materials "as-is" (taken from the samples collected directly from the smelter operations as part of the smelter's QA programme, and therefore as they are experienced by workers), and **objective 3b** looked at the pH of the chemical solutions as used in the study skin tests, after standardisation.

Objective 3a: The proportionate contents of As_2O_3varied from 5% to 98% across the 4 samples. Lead and sulphur were identified as additional potential irritants in the converter baghouse dust and the ETP cake. Both baghouse dusts (ausmelt & converter) had alkaline pH, the As_2O_3sample from the arsenic plant had an acid pH (4.5) and the pH of the ETP sample was close to neutral.

Objective 3b: To remove the confounding effect of disproportional arsenic content across the 4 samples, the samples were standardised to 2g/dL As_2O_3in water. Consequently, the two samples with relatively lower As_2O_3in the source material (converter Baghouse dust & ETP cake) had proportionately increased concentrations of their other constituents after standardisation. These proportionate increases were 19% (ausmelt Baghouse), 373% (converter Baghouse) and 1799% (ETP). Should any of the other constituents be irritants, their irritancies may have been equivalently affected.

Table 14 shows the effects of standardisation on the pH of the samples. The pH for the ausmelt sample went up from pH 7.8 to pH 8.8, the converter sample went from pH 8.7 to pH 9.6 and the ETP sample went from pH 6.7 to 7.8. The arsenic plant sample had a pH of 4.5 after standardisation. Unfortunately, the smelter lab did not provide a pH of the pre-standardised arsenic plant sample. The high pH levels (8.8 & 9.6) or low pH level (4.5) are independently capable of causing irritation.

Study objective 4: To characterise the nature of the dermatological response to these exposures, notably whether the reaction is irritant or allergic, and if prior contact allergy is a risk factor.

The results in section 8.4 show that all the reactions to workplace materials were classified clinically as "irritant". They follow a typical dose-dependent response, with maximal reactions to "neat" solutions, and minimal reactions to highly dilute solutions. The reactions were sharply delineated within the confines of the patch test chambers.

See results & comments in sections 8.4.

Summary and discussion of the results in Table 15.

Note that the results summary is repeated here to facilitate the discussion.

1. The “neat” arsenic concentration is standardised at 2g/dL of arsenic trioxide for all 4 workplace samples.
2. The overall irritancy after standardisation for arsenic trioxide was **ausmelt baghouse dust > converter baghouse dust > ETP cake**. The irritancy of the As_2O_3dust was approximately equal to the ETP cake.
3. The reaction prevalences for all 4 workplace test materials show a graduated response from neat to 1/10, and from 1/10 to 1/100. This is particularly more evident in the ausmelt and converter samples.
4. The concentration-dependent irritancy of pure arsenic trioxide is evident. The irritancy could be because of its moderately low pH (4.5) or because of some other inherent chemical toxicity.
5. Comparison between the arsenic plant and the ETP samples.
    a. The irritancy of neat arsenic trioxide was similar to the irritancy of neat ETP. The irritancy of ETP cannot be explained by its pH, being near neutral (7.8).
    b. As both samples had similar concentrations of arsenic, and pH could not explain the irritancy of ETP, this suggests that the *arsenic* was the cause for the irritancy in both samples.
    c. If any non-arsenic component(s) in the ETP sample had contributed to the irritancy, their combined irritancy would have made ETP more irritant than the pure arsenic sample. As the irritancy of the neat arsenic trioxide was similar to the irritancy of neat ETP, this means the non-arsenic components did not contribute to irritancy. Note that the non-arsenic components of the ETP sample were minimally diluted.
    d. For both samples, the irritancy diminished with increasing dilution. However, the ETP still had some irritancy at higher dilutions (1/100 & 1/1000).
6. Comparison between the arsenic plant sample and ausmelt sample.
    a. Even though the standardisation dilutions were similar for the arsenic plant and ausmelt samples, the irritancy of the ausmelt sample was higher. The main difference between the two was the pH (the ausmelt was strongly alkaline, whereas the arsenic plant was moderately acidic).
7. Comparison between the ausmelt sample & converter sample:
    a. Even though the standardisation dilution was much higher for the ausmelt sample than the converter sample, its irritancy was similar. The main similarities between the two were their similarly high pH and their standardised arsenic content.
    b. The combination of the highly alkaline pH plus the arsenic content of the two baghouse samples will have contributed to their high levels of irritancy.
8. Combining the findings above:
    a. The irritancy of the arsenic plant sample is explained, in part at least, by its pH (acidity), but this does not exclude a contribution from an inherent chemical toxicity to the skin.
    b. The comparison between the arsenic plant and ETP samples showed that the ETP sample’s irritancy was independent of pH, and had no contribution from its non-arsenic component. Hence the ETP sample’s irritancy must be solely due to the arsenic content.
    c. Points 8.a & 8.b suggest that the irritancy of arsenic trioxide is contributed by a low pH (demonstrated by the sample in its pure form) as well as an inherent toxicity to the skin, independent of pH (demonstrated by the arsenic in the ETP sample). The relative contributions of these two characteristics to the irritancy of arsenic trioxide cannot be conclusively ascertained from this study.
    d. The relatively high irritancy of the baghouse samples compared to the ETP and arsenic plant samples is explained by the pH (alkalinity) of their total constituents combined with the inherent irritancy of their arsenic content.
9. Whilst Table 12 (results section on workplace materials analysis) shows significant proportions of lead and sulphur, known skin irritants, the comparative analysis of the arsenic plant and ETP samples (5 above) indicate that the non-arsenic components of the samples contributed minimally to irritancy.

For Table 16, which shows the results of patch tests for workplace materials at varying dilutions for **cases only**, it should be noted that prior analyses of smelter rashes (as stated in the introduction) indicates that the baghouses are the most common locations for rashes. However, the cases in this study were from all the smelter operations.

In Table 17, which shows the results of patch tests for workplace materials at varying dilutions for **controls only**, the reaction prevalences in the control group are also similar to the combined group. A noticeable difference is that there is a big step down in response rates from neat to 1/10 for the ausmelt and converter samples, whereas for arsenic trioxide the difference in minimal. This illustrates the irritancy of arsenic trioxide and underscores the need for exposure prevention for everyone.

Table 18, which compares the reactivity of cases and controls, shows that there was no statistical difference between cases and controls for all four test materials, and at all dilutions. This finding means that prior exposure to the smelter chemicals does not result in sensitisation, including arsenic trioxide. This is important evidence that supports the argument that the smelter chemicals are irritant not allergic.

The data from this study has shown that the reactions to the smelter chemicals are irritant. This conclusion is based on the following:

- The clinical picture of the skin reactions produced under experimental conditions with the patch test materials
- The skin responsiveness increased significantly with increasing concentration of test solutions
- Cases and controls had similar proportions of skin reactivity, indicating that cases were not sensitised.

This is in keeping with the experience of the occupational health staff, whose clinical descriptions of cases suggest irritancy. This has important implications for the smelter in that prevention of irritant contact dermatitis is much easier than for allergic contact dermatitis. On the other hand, this means that exposure prevent is important for everyone, because everyone is potentially vulnerable to irritant reactions.

Whether or not the presence of allergy is a risk factor for experiencing a rash

The presence of allergy was investigated through questions in the interview as well as objectively measured clinical reactions to standardised allergen patch tests.

The data showed the following.

- The cases and controls were not statistically significantly different for pre-existing allergies; although the controls had a higher prevalence of eczema whilst cases had a higher prevalence of urticaria.
- The prevalence of rashes when exposed to metals in jewellery were >3x higher in the case group.
- The two groups were similar for dry skin, itchiness when sweating, acne, greasy skin and rashes when exposed to sunlight.
- The two groups were not statistically significantly different for the frequency of allergic responses to the standardised allergen patch tests, however the direction of difference was suggestive of increased atopy in the cases.

The data suggest that individuals with contact allergy have more reactive skin and that this would predispose them to more severe irritant rashes. The important message from this is that such individuals should be redeployed to workplaces of lesser contact with these production by-products.

Study objective 5: To try to ascertain any causal relationship between baghouse dust (and notably the As_2O_3 in the dust) and the clinical outcomes

This study has demonstrated that arsenic trioxide is irritant through an inherent dermal toxicity as well as its acidic pH. The irritancy of arsenic trioxide in the arsenic plant sample was clearly demonstrable even though it was

significantly diluted during the standardisation process (to 2g/dL). Arsenic plant workers in the real-world setting are exposed to undiluted concentrations of arsenic trioxide dust, which explains the high prevalence of irritant skin reactions amongst workers in this area.

This study has demonstrated that the alkaline pH of baghouse dust confers additional irritancy to that already conferred by the arsenic trioxide present in the dust. This explains the high prevalence of irritant skin reactions amongst workers exposed to baghouse dust.

Comments on the findings of this study in relation to previously published findings

Clinical findings of skin contact with arsenic trioxide

The dermal effects of contact with the arsenic-containing factory materials in this study included redness (starting with faint follicular spots, up to dusky red areas with haemorrhages), vesicles (blisters), pustules, and erosions are typical features of an acute irritant reaction, as described by Frosch, et al [50]. This irritant effect of arsenic is concordant with the findings of Downing (1934)[2], Pinto and McGill (1953)[12], Birmingham et al (1964) [1], Gonçalo (1989) [5] and Mohamed [10].

The only paper describing contact allergic dermatitis in relation to arsenic exposure was by Holmqvist (1951) [7]. Notably, the compounds involved were *sodium arsenite*, *sodium arsenate*, and *arsenic pentoxide*, all of which are highly soluble in water, whereas arsenic trioxide is not. [42, 44, 45]

From the findings of this study and prior publications, the evidence indicates that arsenic trioxide is an irritant, not an allergen. However, other forms or arsenic may produce an allergic response.

Commonly encountered features were the effects of prolonged contact with PPE. The constant use of a respirator causes accumulation of arsenic-contaminated sweat in the contact zones, resulting in irritation & itching. Repeated episodes lead to increased pigmentation. This was also described by Pinto and McGill (1953)[12], Birmingham et al (1964) [1], Gonçalo (1989) [5] and Mohamed [10]. Interestingly, there were no cases with features of hyperkeratosis, despite long-term exposures to levels above the occupational exposure limit. This was also found by Pinto and McGill (1953)[12].

Whilst community studies have demonstrated a dose-response relationship between the amount of arsenic exposure and the frequency of various skin lesions (Hall, et al [23], Ahsan et al [16], Haque et al [24], Rahman et al [30,31], and Roychowdhury [33]), a detailed investigation by Smith et al [37], who accounted more carefully for long term exposure, found that the characteristic skin lesions required arsenic exposures in drinking water of greater than 100-200µg/L, and an average latency of 23 years since first exposure. [38]. Perhaps this explains the lack of cases of classic chronic arsenicosis in occupationally exposed workers, as it would be extremely unusual for workers to be exposed to such levels constantly, over such a long time.

Whilst perforation of the nasal mucosa was not specifically examined for as it was not an objective of the study, this was not reported by any of the participants.

Patch test technique

The literature revealed little on the patch test techniques used by previous researchers. Birmingham et al (1964) [1] dissolved 5% arsenic in starch. Gonçalo (1989) [5] used dilutions of 5%, 2% and 1% in petrolatum. The details of the test technique used by Holmqvist (1951) [7] could not be found. For this study, a solution of arsenic trioxide in water was used. Owing to the slow dissolution in water[46], the samples of factory material were placed in water several weeks prior to testing, to achieve equilibrium. The option to use a “neat” solution of 2.1g/100ml at 25°C, then dilutions of 1:10, 1:100 and 1:1000 worked well, and produced interpretable dose-dependent results.

Limitations

Participant sample size (cases & controls)

The sample size is small because cases are relatively rare, and the patch testing procedure is onerous. Nonetheless, the study was able to draw significant conclusions from the findings.

Responses to Questionnaire

Whilst the denominators in Tables 1 to 6 were mostly very close to the totals for Cases & Controls, Table 7 (PPE use) had varying denominators, especially in the responses from the Controls. The 3 questions with poor responses related to the use of “mutton cloth”, masks and full body suits. Poor responses to “mutton cloth” were probably because the use of mutton cloth is discouraged by management, as it interferes with the protective function of respirators. The poor responses to “mask” use were probably because the term is ambiguous, and the respondents were unclear if the question related to “respirators” or something else. On review, this question should not have been included. The poor responses to “full body suit” use is not clear. However, these suits are only used by workers in the arsenic plant whilst doing maintenance work in the kitchens, so it is likely that many of the respondents were entirely unfamiliar with the term and therefore did not respond.

The responses for Table 8 were based on memory. No response means the individual could not remember. The low response rates of the rainy/dry and windy/still questions reduce the interpretability of these answers.

A further limitation related to the responses to the questions of this study was that this type of information was dependent on accurate answers given by the study participants - there was no realistic opportunity to fully interrogate the veracity of the answers given. This is further addressed under Study Objective 1 in the discussion.

Workplace materials samples

Only one bulk sample was used from each worksite. Whilst it is recognised that concentrations of compounds can vary from the same worksite day by day, the production process at the smelter remains constant with minimal variability. The use of bulk sampling (collected from a general work area as opposed to a specific point location) reduces day to day variability.

The workplace material samples that were tested by Chemtek were not the exact samples used for patch testing. Unfortunately, the samples used for patch testing were mislaid by the smelter laboratory, and other samples had to be used. These other samples came from the identical workplaces as the samples used for patch testing.

Potential misclassification of irritant and allergic patch test reactions.

Even though the participants were instructed to avoid getting the test strips wet, 4 of the participants allowed their strips to get wet, adversely impacting their interpretability.

Of those who had allergic reactions, 4 were mild and therefore equivocal. These were not the same participants in which the strips had got wet, impacting their interpretation. These equivocal responses were not included as positives in the results.

10 CONCLUDING COMMENTS

This study has answered several questions regarding the relationships between the “arsenic rash” and the workplace materials examined, specifically arsenic trioxide, baghouse dust and the “cake” produced by the effluent treatment plant.

The main finding is that arsenic trioxide is an irritant not an allergen, because of its low pH as well as an inherent dermal toxicity. The presence of arsenic trioxide in the baghouse dust and ETP cake confers irritancy to these operational materials. The baghouse dusts are additionally irritant because of their high pH.

Irritancy has implications for exposure prevention, in that all employees are potentially affected, not only a subset of vulnerable people.

Whilst the data did not demonstrate statistical significance due to small numbers, it suggests that individuals with contact allergy have more reactive skin and that this would predispose them to more severe irritant rashes. This

has additional implications on exposure prevention, in that individuals with contact allergy should preferably not be deployed to tasks involving overt exposure to these operational materials.

There was no difference between cases and controls for skin hygiene practices (washing and use of protective creams). These could be the result of a bias whereby employees wish to please and appear compliant with company policy and conscientious with regard to cleanliness.

The question of the contribution from PPE to the development of skin rashes was partly answered; whilst the general screening PPE related questions (to cases and controls) did not show specific causal relationships, many case participants indicated that respirator use was linked to rashes in the head and neck area. .

11 RECOMMENDATIONS

The following represent areas of consideration, preferably in interactive discussions with smelter staff (industrial hygienist, operations management, and occupational health), from which further actions may be planned.

Skin hygiene practices

Good skin hygiene practices are an important mainstay of any workplace skin protection programme. This includes handwashing and, where possible, avoidance of contact with irritants. These practices should continue. The use of a protective hand cream should be reconsidered, as it showed no protective effect, and may introduce a false sense of security. Furthermore, smelter records indicate that rashes affect the hands infrequently (only 6% of the 486 cases reported).

Use of PPE

Where PPE is causing significant discomfort through skin occlusion and increasing sweatiness, the benefits of its use should be examined. A particular issue seems to relate to respirator use. The clean-shaven policy is widely recognised as correct practice, but its efficacy for protection should be measured against the protection achieved with a light growth of facial hair, and/or the use of mutton cloth. It is possible that, at least for certain employees, shaving leads to skin conditions (acne and sycosis barbae) that adversely impact the efficacy of the respirator. Ultimately, the most effective solution is to engineer away the exposure thereby eliminating the need for occlusive PPE.

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13 Appendix 1: Consent Form

University of Cape Town
Faculty of Health Sciences

INFORMED CONSENT TO PARTICIPATE IN A STUDY OF THE SKIN RASHES TAKING PLACE AT THE SMELTER

PARTICIPANT INFORMATION SHEET

1. **Title of research project**

   Assessment of the skin rashes affecting employees of the smelter, to better understand the nature of the rashes, and their possible connection with arsenic dust and baghouse dust.

2. **Names of the researchers**

   Professor Emeritus Jonathan Myers, Centre for Environmental and Occupational Health Research, Department of Community Health, University of Cape Town.

   Dr Greg Kew, Centre for Environmental and Occupational Health Research, Department of Community Health, University of Cape Town.

   Sr Erna Schreuder, Professional Nurse, Smelter's Occupational Health Service.

3. **Purpose of the research**

   We wish to ask you to participate in a scientific study of the skin rashes affecting employees at the smelter, and their possible relationship with arsenic dust and baghouse dust.

   The importance of the study is that it will help us to better understand the causes of the skin rashes, and therefore improve the Smelter's efforts to prevent them from taking place.

4. **Description of the research project**

   The study comprises two phases.

   In the 1st phase, we are inviting employees who experienced a skin rash during 2016 and 2017 to participate in this study, and we are going to compare them to similarly exposed workers who did not experience a rash during the same period (called "controls"). So these workers will be examined because they experienced a rash in the past (2016 & 2017)

   We will ask you questions about your general health, the skin rash and the circumstances that led to the rash. We will apply a special patch to your skin, in which there are small quantities chemicals including arsenic plant dust (pure arsenic) and baghouse dust (a mixture from the copper smelter). We need to see if exposure

to any of these chemicals results in a reaction in your skin.

In the 2nd phase, which will start after completion of the 1st phase, we will invite all employees who experience a skin rash, at the time when the rash occurs, for an assessment. This will include an interview, an examination and a blood test; a patch test will also be done, but this will only be a few weeks after the rash has settled.

The participants in the 2nd phase will not be the same as those in the second study. However, this consent form is the same for participants in the 1st phase as for the 2nd phase.

5. Risks and discomforts of the research

The skin patch test will be on your skin for 3 days and may result in some mild itchiness during that time, depending on whether you react to any one of the substances in the patch. If you experience any symptoms, they are temporary, and will recover quickly after the test, because the chemicals used in the patch test are in very small quantities. In the unlikely event that you experience more discomfort than mild itchiness, we will remove the patch immediately, to allow your skin to settle. There will be no lasting effects of the testing. The blood test (in phase 2 only) will require in a small needle to be inserted into a vein to obtain a blood sample.

UCT carries a No Fault Insurance Policy to cover non-commercially sponsored interventional clinical research. No Fault compensation implies that participants incurring a research-related injury are not required to prove wrong-doing to be compensated.

6. Expected benefits to you and to others

The results of the study will help the smelter to better understand the links between the workplace and the skin rashes, the aim of which is to implement better ways to prevent them from taking place. The personal benefits for you will be that you will better understand the nature and cause of the rash, and therefore more effectively be able to prevent it from happening in future. The results of the study will also assist your doctor to treat your skin condition more effectively.

7. Costs to you resulting from participation in the study

The study is offered at no cost to you. In the event an allergy is discovered and you wish to be seen by a doctor for it, we can recommend to you who to see. However, any additional costs of such medical visits or treatments will not be the responsibility of the study team, unless they are to provide temporary treatment of a skin reaction caused by the patch skin test.

8. Confidentiality of information collected

You will not be identified in any reports on this study. The records of all test results and the questionnaires will be kept completely confidential and will be seen only by members of the study team. However, should you be found to have a work-related allergy, this is an occupational disease and we will encourage you to inform the occupational health practitioner, so that steps can be taken to ensure that you are adequately protected at work.

9. Voluntary nature of participation

Your participation in this project is entirely voluntary. Even after you give your consent, you may refuse to participate in or withdraw from the study at any time without penalty or loss of benefits. Refusal to take part

in the study, or withdrawal from the study, will not affect current or future employment at the smelter.

10. **Independence of the researchers**
Although the smelter is funding the research, the independence of the researchers in planning and doing the research, and in the analysis and interpretation of the data collected, including being able to present and publish the findings in scientific settings and scientific media will be protected in a research agreement between DPM and the researchers.

11. Documentation of the consent

One copy of this document will be kept together with our research records on this study. A second copy will be given to you to keep.

12. Contact person.

You may contact the following person for answers to further questions about the research, your rights, or any injury you may feel is related to the study. Name of person Dr Greg Kew Telephone No +27 82 553-0316. An additional person to contact is the principal investigator, Prof Jonny Myers Telephone No +27 82 926 8925.

13. Contact details of the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee (HREC).

You may contact the HREC if you have any ethical concerns, or questions about your rights or welfare about participating in this study. The contact details are: Room E53-46, Old Main Building, Groote Schuur Hospital, Observatory, 7925, Western Cape, South Africa. Telephone: +27 21 404-7682.

PARTICIPANT CONSENT

I have read [or been informed] of the information given above. I understand the meaning of this information. Prof./Dr./Mr./Ms. _____ has offered to answer any questions I may have concerning the study. I hereby consent to participate in the study.

_____ _____

Printed name of participant Participant signature

_____ _____

Witness (Print) Witness signature

DATE: _____

14 Appendix 2: Questionnaire

Contact Dermatitis Questionnaire and Evaluation

PERSONAL DETAILS

SUBJECT NUMBER:	GENDER: Male / Female	DATE OF TEST:
DATE OF BIRTH:	DATE EMPLOYED:	
OCCUPATION / JOB?		COMPANY
WHERE DO YOU WORK IN THE SMELTER?		DEPARTMENT

MEDICAL HISTORY

1.	Do you have any past history of allergies? (Circle choice.) DON'T KNOW / NOT SURE = 0 YES=1 NO=2 If yes, what	☐
2.	Have you ever had any of the following, NOT caused by your work: (Please circle Yes or No. If not sure, leave blank) 1. Asthma (a weezy or tight chest)? YES=1 / NO=2 2. Hay fever (sneezing & runny nose) YES=1 / NO=2 3. Eczema (itchy skin involving flexures of elbows, wrist, behind knees) (show subject) YES=1 / NO=2 4. Urticaria / hives (warm, red, itchy) (bommels) YES=1 / NO=2 5. Allergy affecting eyes (red itchy eyes) YES=1 / NO=2 6. Any other allergies YES=1 / NO=2 (If yes, write down what else you are allergic to)	☐ ☐ ☐ ☐ ☐ ☐
3.	Is there anything that makes condition(s) above worse? (Please circe your choice. More than one is acceptable. If not sure, leave blank.) 1. time of day YES=1 / NO=2 ☐ 2. certain foods/drinks YES=1 / NO=2 ☐ 3. pets, animals YES=1 / NO=2 ☐ 4. dust, fumes, smoke YES=1 / NO=2 ☐ 5. weather YES=1 / NO=2 ☐ 6. seasons YES=1 / NO=2 ☐ 7. grass, pollens, etc YES=1 / NO=2 ☐ 8. anything else? YES=1 / NO=2 ☐ Notes:	
4.	Has a doctor ever diagnosed you with an allergy? (If not sure, leave blank) YES=1 NO=2 If so, what?	☐
5.	Do you get a rash from metal buttons, metal fasteners, metal costume jewelry (for example earrings) or other metal objects next to your skin? YES=1 NO=2	☐
6.	Do you have dry skin? YES=1 NO=2	☐
7.	Does your skin itch when you sweat? YES=1 NO=2	☐

8.	Other medical problems: 1. Do you ever get a rash on the face, not caused by work? YES=1 / NO=2 2. Do you ever get pimples / acne ("puisies") YES=1 / NO=2 3. Do you have a greasy skin? YES=1 / NO=2 4. Does the sun cause a rash? YES=1 / NO=2 Any other skin problem(s) …… Any other medical problem(s) …… …… … Are you on any regular medications? If so, please record these here. …… …	☐ ☐ ☐ ☐

Space for additional notes if necessary overleaf: (indicate the number of the question you are answering)

Workplace Skin Management & Hygiene Practices

9.	At work, do you wash your hands after coming into contact with dust or chemicals? YES=1 / NO=2 1. If yes, how often, in a day, do you wash your hands at work? …… 2. If no why not? ……	☐
10.	Do you use soap when you wash your hands? YES=1 / NO=2 1. If yes, is this the soap supplied by the work, or your own? Work = 1 / Own = 2 2. If no, why not? ……	☐ ☐
11.	Do you you wash your hands before going to the toilet? YES=1 / NO=2 1. If no, why not? ……	☐
12.	Do you use a protective cream to protect your skin at work? YES=1 / NO=2 1. If yes, and you know the name of the product, please write it here: …….. 2. If no, why not? ……	☐

Use of Personal Protective Equipment (PPE) (Leave blank if not applicable)

13.	PPE used	When introduced? (Circle answer)	How often used?
	1. Head gear / helmet	From starting work at smelter =1/ Afterwards=2 ☐	_____ hours per day
	2. Overalls	From starting work at smelter =1 / Afterwards=2 ☐	_____ hours per day
	3. Protective glasses	From starting work at smelter =1 / Afterwards=2 ☐	_____ hours per day
	4. Gloves	From starting work at smelter =1 / Afterwards=2 ☐	_____ hours per day
	5. Boots / shoes	From starting work at smelter =1 / Afterwards=2 ☐	_____ hours per day
	6. Mutton cloth	From starting work at smelter =1 / Afterwards=2 ☐	_____ hours per day

13.	PPE used	When introduced? (Circle answer)	How often used?
	7. Mask	From starting work at smelter =1 / Afterwards=2 ☐	_____ hours per day
	8. Respirator	From starting work at smelter =1 / Afterwards=2 ☐	_____ hours per day
	9. Full body suit	From starting work at smelter =1 / Afterwards=2 ☐	_____ hours per day
	10. Other	From starting work at smelter =1 / Afterwards=2 ☐	_____ hours per day

14.	PPE used	How maintained / cleaned	If any of the listed PPE items are shared with other workers, mark the block with an "X"
	1. Head gear / helmet		☐
	2. Overalls		☐
	3. Protective glasses		☐
	4. Gloves		☐
	5. Boots / shoes		☐
	6. Mutton cloth		☐
	7. Mask		☐
	8. Respirator		☐
	9. Full body suit		☐
	10. Other		☐

Rashes at Work

15.	Have you had a rash caused by your work? If yes, proceed to question 6. If no, proceed to question 7. YES=1 / NO=2	☐

Controls only (workers who have not had a rash at work)

16.	Why do you think you didn't get a rash at work? …… …… …… …… ……

CONTROLS PROCEED DIRECTLY TO CLINICAL EXAMINATION

Cases only (workers who have had a rash at work)

Description of the most recent incident when the skin rash occurred

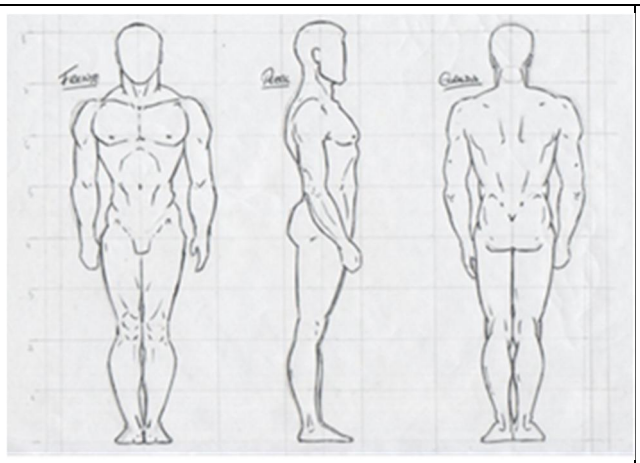
17.	When was the last time that you had a skin rash? (the date, or if you are not sure, approximately when) _____
18.	Was this the first time that this rash happened at work? YES=1 / NO=2 ☐ If No, how many times had it happened before? _____
19.	Briefly describe the last (most recent) incident. (what work were you doing, and what happened?): …… …… …… …… …… ……
20.	When you got the rash, was the weather: 1. Hot=1 / Cold=2 ☐ 2. Rainy=1 / Dry=2 ☐ 3. Windy=1 / Still=2 ☐
21.	What type of work were you doing when you got the rash? (Please choose only ONE. Circle your choice) ☐ Routine normal work = 1 Clean-up work = 2 Upset / shutdown work = 3
22.	When you got the rash, were you using a cream to protect your skin at the time? YES=1 / NO=2 ☐ If you know the name of the product, please write it here: ……
23.	When you got the rash, were you using the standard PPE at the time? YES=1 / NO=2 ☐ 1. If No, are you using less than the standard PPE; YES=1 / NO=2 ☐ 2. If so, why …… 3. If No, are you using anything extra to the standard PPE at the time? YES=1 / NO=2 ☐ 4. If yes, why ……

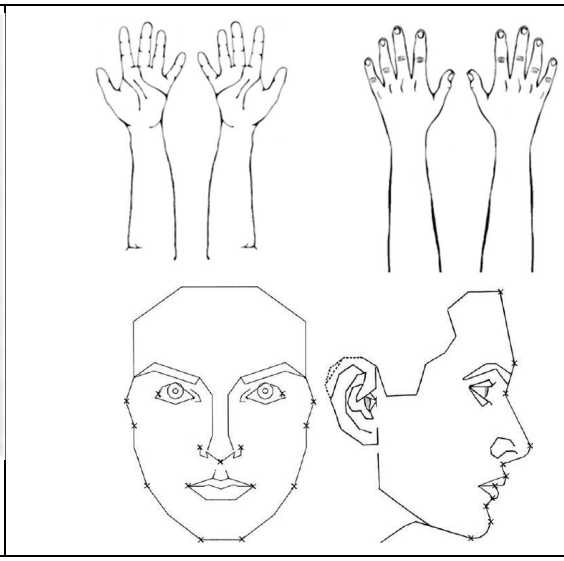
24.	Do you think any of the following PPE items are causing the skin rash? If yes, mark with an "X", and explain briefly why you say this)	
☐	1. Head gear / helmet	
☐	2. Overalls	
☐	3. Protective glasses	
☐	4. Gloves	
☐	5. Boots / shoes	
☐	6. Mutton cloth	
☐	7. Mask	
☐	8. Respirator	
☐	9. Full body suit	
☐	10. Other	

25. What parts of the body were affected? (Please mark with an "X" and draw on the images below.)

1.	At point of respirator / mask contact ☐	5.	Neck ☐	9.	Back ☐
2.	Nose / nostrils ☐	6.	Forearms ☐	10.	Chest ☐
3.	Around eyes ☐	7.	Hands ☐	11.	Legs ☐
4.	Rest of the face ☐	8.	Groins ☐	12.	Other ☐

26.





27. Which of the following did you experience?

1.	Redness ☐	4.	Itchy ☐	7.	Burning, prickling, or stinging ☐
2.	Change in the skin colour ☐	5.	Wet and weeping ☐	8.	Dry skin ☐
3.	Painful ☐	6.	Can you feel the rash with your fingers, when you touch the skin (not flat on the skin)? ☐	9.	Scaly / flaky / roughness ☐

28. Did your rash: heal on it's own =1 / require medical treatment to make it go away =2 ? (Please circle) ☐

29. Did you need to see a doctor for treatment? (Please circle) YES=1 / NO=2 ☐

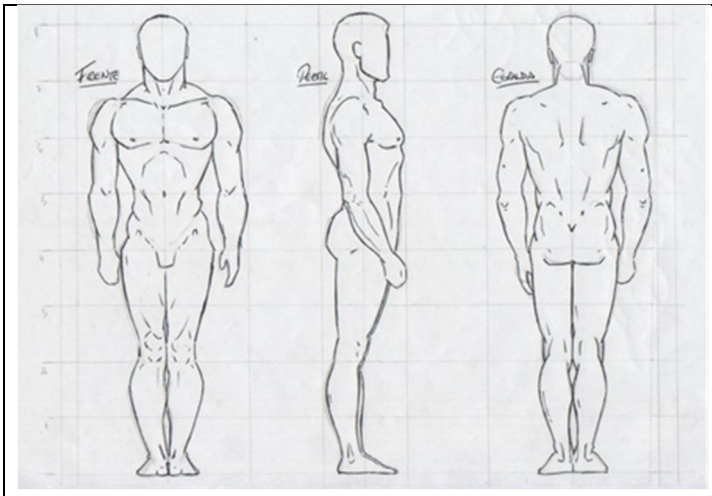
30. How long did it take for the rash to go away? _____ days

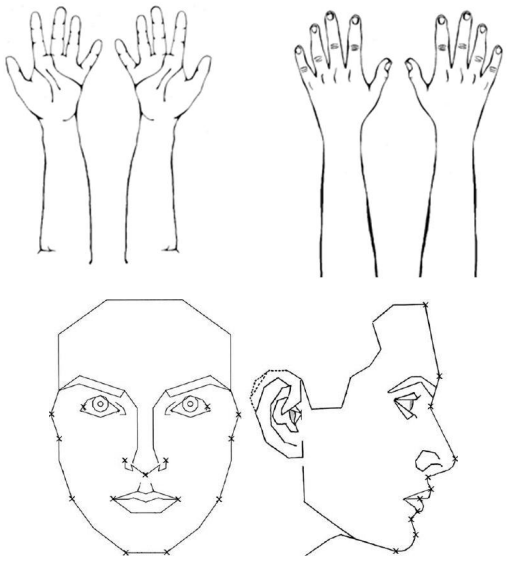
If you have had the rash more than once

31.	If you have had the rash more than once, is it always the same? (Please circle. If no, explain) YES=1 / NO=2 ☐ …… …… …… …… …… ……

CLINICAL EXAMINATION

LESION DISTRIBUTION

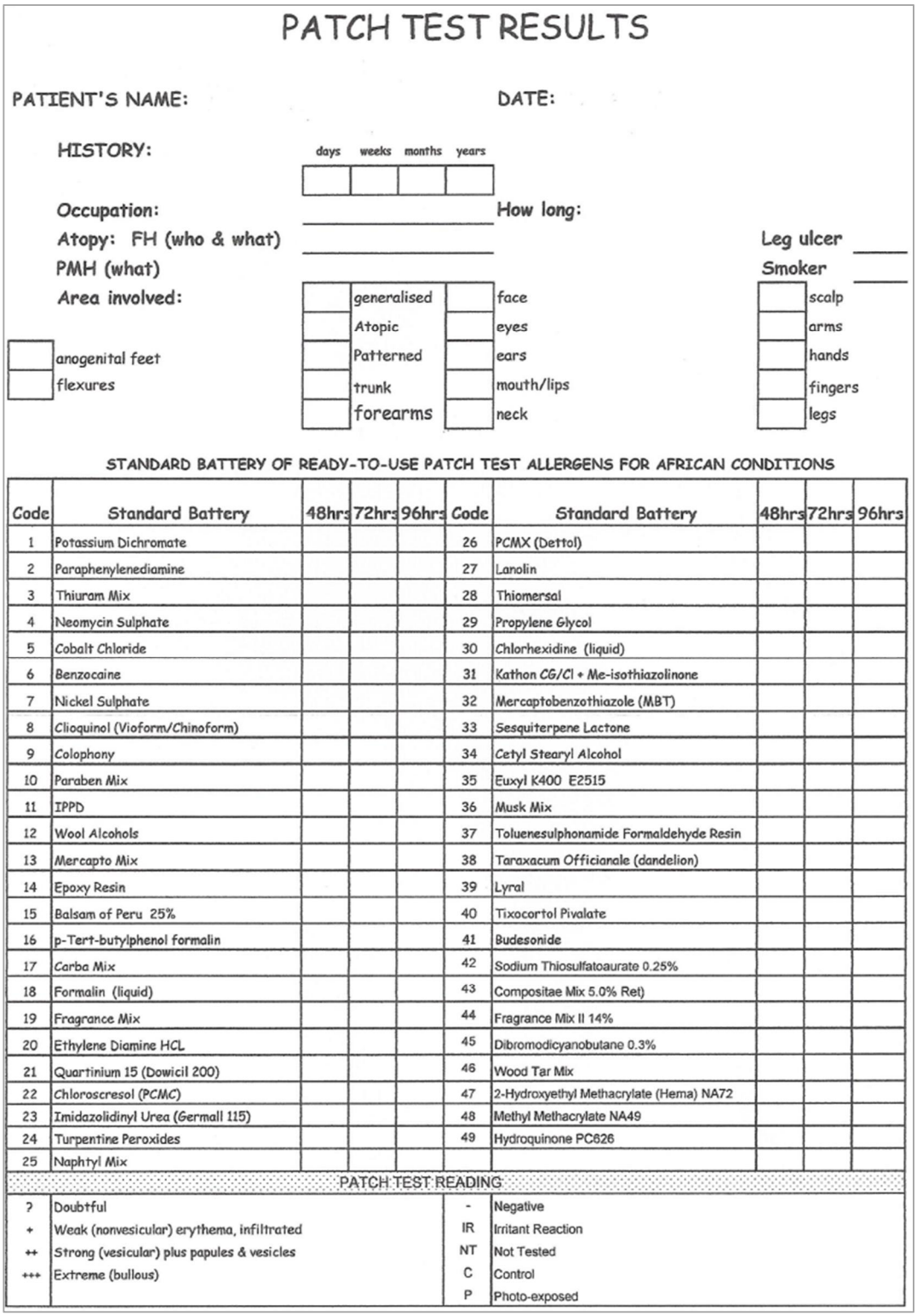




PATCH TEST RESULTS (SEE SEPARATE SHEET)

15 Appendix 3: Standard Allergen Patch Test results sheet

Figure 11: Standard Allergen Patch Test results sheet



PATCH TEST RESULTS

PATIENT'S NAME: DATE:

HISTORY: days weeks months years

Occupation: How long:

Atopy: FH (who & what)

PMH (what)

Area involved:

☐ generalised ☐ face ☐ scalp

☐ Atopic ☐ eyes ☐ arms

☐ anogenital feet ☐ Patterned ☐ ears ☐ hands

☐ flexures ☐ trunk ☐ mouth/lips ☐ fingers

☐ forearms ☐ neck ☐ legs

Leg ulcer ____

Smoker ____

STANDARD BATTERY OF READY-TO-USE PATCH TEST ALLERGENS FOR AFRICAN CONDITIONS

Code	Standard Battery	48hrs	72hrs	96hrs	Code	Standard Battery	48hrs	72hrs	96hrs
1	Potassium Dichromate				26	PCMX (Dettol)			
2	Paraphenylenediamine				27	Lanolin			
3	Thiuram Mix				28	Thiomersal			
4	Neomycin Sulphate				29	Propylene Glycol			
5	Cobalt Chloride				30	Chlorhexidine (liquid)			
6	Benzocaine				31	Kathon CG/Cl + Me-isothiazolinone			
7	Nickel Sulphate				32	Mercaptobenzothiazole (MBT)			
8	Clioquinol (Vioform/Chinoform)				33	Sesquiterpene Lactone			
9	Colophony				34	Cetyl Stearyl Alcohol			
10	Paraben Mix				35	Euxyl K400 E2515			
11	IPPD				36	Musk Mix			
12	Wool Alcohols				37	Toluenesulphonamide Formaldehyde Resin			
13	Mercapto Mix				38	Taraxacum Officianale (dandelion)			
14	Epoxy Resin				39	Lyral			
15	Balsam of Peru 25%				40	Tixocortol Pivalate			
16	p-Tert-butylphenol formalin				41	Budesonide			
17	Carba Mix				42	Sodium Thiosulfatoaurate 0.25%			
18	Formalin (liquid)				43	Compositae Mix 5.0% Ret)			
19	Fragrance Mix				44	Fragrance Mix II 14%			
20	Ethylene Diamine HCL				45	Dibromodicyanobutane 0.3%			
21	Quartinium 15 (Dowicil 200)				46	Wood Tar Mix			
22	Chloroscresol (PCMC)				47	2-Hydroxyethyl Methacrylate (Hema) NA72			
23	Imidazolidinyl Urea (Germall 115)				48	Methyl Methacrylate NA49			
24	Turpentine Peroxides				49	Hydroquinone PC626			
25	Naphtyl Mix								

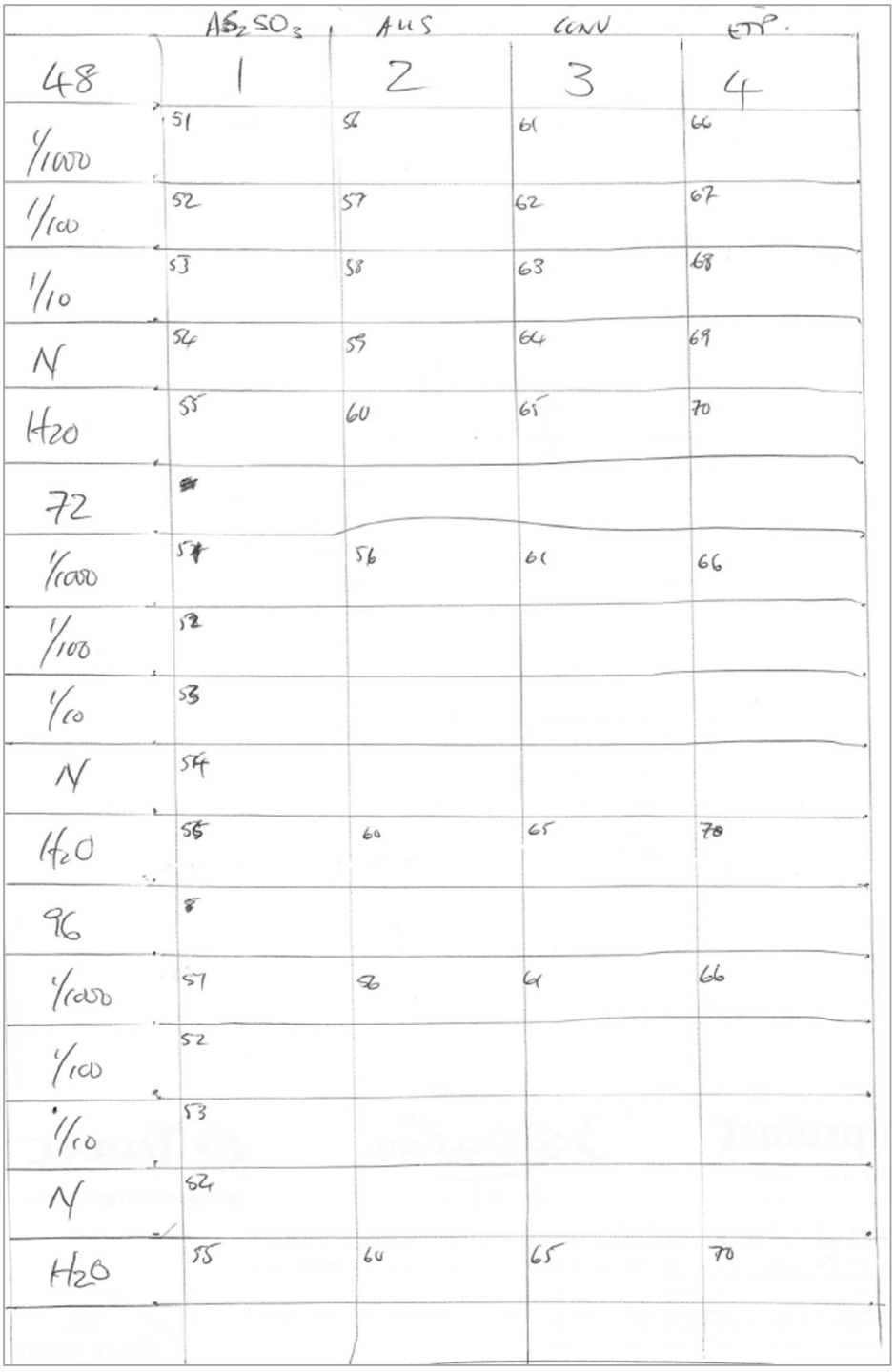
PATCH TEST READING

?	Doubtful	-	Negative
+	Weak (nonvesicular) erythema, infiltrated	IR	Irritant Reaction
++	Strong (vesicular) plus papules & vesicles	NT	Not Tested
+++	Extreme (bullous)	C	Control
		P	Photo-exposed

16 Appendix 4: Workplace Sample Patch Test results sheet

See explanatory notes in Appendix 5 “on the day of testing”.

Figure 12: Workplace Sample Patch Test results sheet



	AS_2SO_3	AUS	CONV	ETP.
48	1	2	3	4
1/1000	51	56	61	66
1/100	52	57	62	67
1/10	53	58	63	68
N	54	59	64	69
H_2O	55	60	65	70
72				
1/1000	56	56	61	66
1/100	52			
1/10	53			
N	54			
H_2O	55	60	65	70
96				
1/1000	57	56	64	66
1/100	52			
1/10	53			
N	54			
H_2O	55	60	65	70

17 Appendix 5: Technical details of the patch test procedure

This section describes in detail the patch testing procedure. This is important, given the paucity of information in the scientific literature on arsenic patch testing.

The sample preparation, application and interpretation was conducted by or under the supervision of an experienced specialist dermatologist (Prof Gail Todd).

Testing strips and patch test chambers from Mednom were used. These comprised:

- Pre-prepared strips comprised allergens known to be common in South African workplaces, as recommended by the University of Cape Town (appendix 2) This comprised 45 allergens in the 2017 session and was increased to 49 chambers in the 2018 testing session.
- Test strips with chambers into which the researchers placed varying dilutions of 4 selected workplace materials.

Figure 13: Test strips & pre-filled test chambers used for allergen testing

Tests strips and chambers containing allergens, in their enclosures as packaged	Tests strips and chambers containing allergens, in their enclosures opened for application
	

Figure 14: Test strips & empty test chambers used for testing the workplace material samples

Van der Bend test strips with test chambers, prior to charging with workplace material test solution	Finn test strips with test chambers, prior to charging with workplace material test solution
	

The skin was wiped gently with ether prior to the patches being applied to remove natural skin oils to improve sticking of the patch tests. No participant's back was so hairy as to require shaving 24-48 hours before testing to optimize the sticking of the tape[14].

Using a skin marker pen, the chamber numbers were recorded on the skin alongside the test strips, to facilitate matching skin reactions to the appropriate allergen, after 72 – 96 hours.

Study subjects are transferred out of heavy manual work for the duration of the time period that they were carrying the patch tests. They were interviewed briefly after 24 hours, to ascertain if they were experiencing symptoms related to the skin patches (to enable early intervention in the event of significant symptoms). After the final reading, if any significant allergic reactions were noted, a mild cortisone cream was applied to the affected skin.

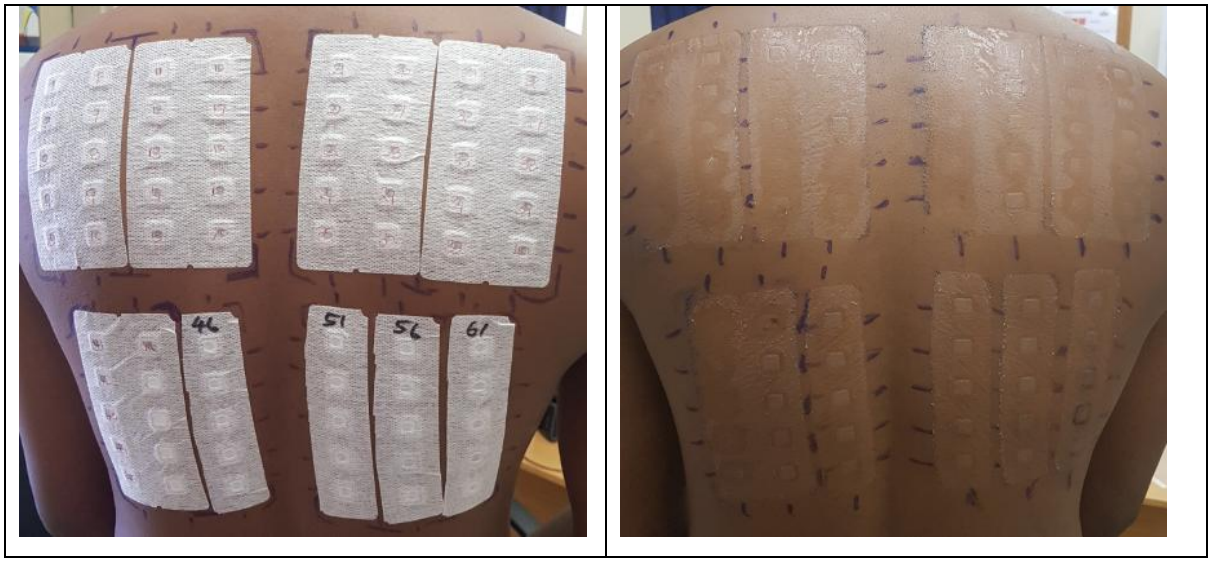
Study participants were counselled to report any adverse skin reactions. They were instructed to report back to the researchers after 24 hours (symptom feedback and early intervention if necessary), 48 hours (removal of strips and interim skin assessment), and at 72 hours (skin reading). Were appropriate (evolving skin reactions), a further skin reading was done at 96 hours.

For the few who experienced itchy reactions a mild corticosteroid cream was applied to the affected skin after the final reading.

The general procedure was as follows:

- The smelter's OH staff made the necessary arrangements for the participants to be presented to the dermatologist on the Monday & Tuesday of the assessment week.
- The dermatologist clinically assessed the cases and supervised the application of the patch tests.
- The patch tests were formally read after 72 hours (some again at 96 hours), on the Thursday and Friday (some on the Saturday).
- This continued until 50 cases were assessed. Given the burden of work, the exercise was conducted over 2 sessions; one in Dec 2017 and the next in Oct 2018.

Figure 15: Patch tests on the back of a study participant and appearance immediately after removal

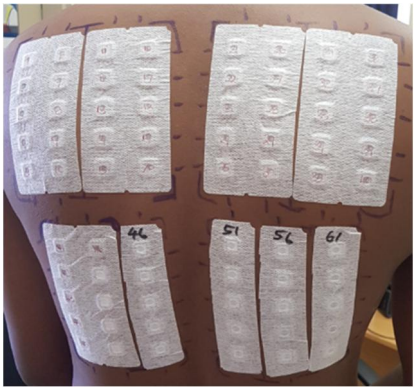


In the image above, the double strips contain the pre-prepared standard allergens, and the single strips contain the dilutions of the workplace material samples.

Table 21: Distribution, labelling & numbering of skin test strip chambers (2017 test session)

Workplace material source	Chamber No Neat solution	Chamber No 1:10 dilution	Chamber No 1:100 dilution	Chamber No 1:1000 dilution	Chamber No Water (control)
Arsenic trioxide ("Ars")	**46**	**47**	**48**	**49**	**50**
Ausmelt bag house ("Aus")	**51**	**52**	**53**	**54**	**55**
Effluent treatment plant ("ETP")	**56**	**57**	**58**	**59**	**60**
Converter bag house ("Con")	**61**	**62**	**63**	**64**	**65**

Figure 16: Skin test strips placed on the study participant, labelled and marked

Numbering in 2017 (46-65)	Numbering in 2018 (51-70)
	

18 Appendix 6: Preparation of workplace material samples for patch testing

Although there is little information for patch testing with Arsenic, the available scientific literature described a technique using samples prepared in petroleum jelly and in corn starch (Gonçalo et a[5]). They used samples categorised as follows: materials as they are used in the workplace ("as-is"), and at the following dilutions; 1%, 2% and 5% dilution.

For this study, the researchers determined that it would be preferable to use distilled water as the diluent, as this would make the arsenic & other constituents in the workplace dust more bioavailable to the skin. Furthermore, this more closely matches the true workplace circumstances.

Workplace test samples were obtained from the following sites:

- Dust from the arsenic plant (98% arsenic)
- Dust from the converter bag house (8-9% arsenic)
- Dust from the ausmelt bag house (28-46% arsenic)
- Filter "cake" from the effluent treatment plant (11-13% arsenic)

Arsenic occurs as inorganic arsenic trioxide in this smelter. The solubility of arsenic trioxide in water is 2.1g/100ml [46]. This was used as the reference point for a "neat" As_2O_3 solution, as well as neat solutions of dust from other locations in the workplace; all the neat solutions were standardised to an arsenic level of 2g/100ml.

The detailed chemical constituents of these workplace material samples are listed in the results section.

One week prior to testing, the smelter QA laboratory obtained workplace materials from the arsenic plant (As_2O_3), converter baghouse, ausmelt baghouse and ETP cake. These samples were analysed, and the chemical constituents expressed as percentages of the sample (g/g). To standardise the samples to 2.1g/100ml, the appropriate quantities (grams) of material dissolved in distilled water to yield the 2.1g/100ml concentration. These were the "neat" samples to be used for testing. The pH values and chemical constituents of these solutions were measured - see results section for these values. This preparation of the "neat" solutions one week ahead of the skin testing was to allow time for the arsenic trioxide to dissolve.

One day prior to testing, the researchers prepared the workplace material skin testing solutions as follows. The neat samples were diluted to 1:10, 1:100 and 1:1000 for each workplace, using a pipette, as follows:

- 1ml of "neat" solution was added to 9ml distilled water to yield a 1:10 dilution
- 1ml of the 1:10 dilution was added to 9ml of distilled water to yield a 1:100 dilution
- 1ml of the 1:100 dilution was added to 9ml of distilled water to yield a 1:1000 dilution

Figure 17: Neat solutions of workplace material samples and the test solution bottles

4 neat solutions of workplace materials supplied by the lab (blue caps) (standardised to 2g/100ml arsenic)	The lab neat solutions (blue caps) were transferred into the wokplace material test solution bottles (green caps), from which the dilutions were made

One the day of testing, just prior to each participant being tested, the workplace material test solutions were transferred from the workplace material test solution bottles (**green caps**) to the chambers in the skin test strips, which would then be placed on the backs of the study participants.

Figure 18: Transfer of the diluted workplace material test solutions to the skin test strips

Here the workplace solutions are being tested for pH using litmus paper. Thereafter the solutions are transferred to the chambers in the test strips using a pippete.

These are the chambers in the skin test strips, ready for transfer to the back of a study participant. Notice the filter paper, which absorbs and holds the solution and workplace chemical.

Care has to be taken to prevent the filter paper (& test chemical) from falling out whilst placing the strip onto the study participant's skin.

Hence, for each participant, there were 4 solutions for each workplace material sample (neat, 1:10, 1:100 & 1:1000). Given that there were 4 workplace material samples tested, each participant would have 4x4=16 test solutions applied. In addition, each workplace material sample required a test control, in the form of plain water, thereby resulting in a total of 20 tests per participant.

Prior to transfer to the skin test strips, the pH of the neat workplace solutions was re-tested using litmus paper, to ensure that none of the solutions would be so acid or alkaline as to put the participants at risk. The pH values varied from 4.5 (As_2O_3) to 8.5 (ausmelt & converter). These values were deemed safe in small quantities. See results for more details.

These test solutions were each placed carefully into test "chambers" in specially designed test strips, which were carefully labelled, according to the chamber numbers in the table below. The test chamber numbers started at the next number after the last allergen. In 2017 there were 45 allergens, so it was agreed to number the first workplace material test chamber 46. This convention was retained in 2018; there were 49 allergens, so the first workplace material test chamber was numbered 50.

19 Appendix 7: Approval from UCT Health Research Ethics Committee (UCT HREC)

RESEARCH ETHICS COMMITTEE
04 DEC 2020
FACULTY OF HEALTH SCIENCES
UNIVERSITY OF CAPE TOWN
Human Research Ethics Committee

UNIVERSITY OF CAPE TOWN

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.11.21
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	7/12/20

Comments to PI from the HREC

Principal investigator to complete the following:

1. Protocol information

Date (when submitting this form)	3 December 2020		
HREC REF Number	261/2016	Current Ethics Approval was granted until	30/11/2020
Protocol title	A study to characterize the "arsenic rash" observed at a copper smelter in Tsumeb, Namibia (MSc Med Canddiate; Dr Greg Kew)		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	☐ Yes ☐ ✓No		
If yes, could you please provide the HREC Ref's for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	EMERITUS PROFESSOR J MYERS		
Department / Office Internal Mail Address	CENTRE FOR ENVIRONMENTAL AND OCCUPATIONAL HEALTH RESEARCH, DEPARTMENT OF PUBLIC HEALTH & FAMILY MEDICINE		

21 February 2019 Page 1 of 5 FHS016

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

1.1 Does this protocol receive US Federal funding?	☐ Yes	☐✓ No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval? **Note:** Any annual approvals for **Full Committee** review MUST be submitted on the monthly HREC submission dates. (Please send electronic copy for full committee review to hrec-enquiries@uct.ac.za)	☐ Yes	☐ No
If yes in 1.2 please complete section 1.3 below for invoicing purposes		
1.3 Annual Approval for **full committee** review	- R 3450 (inclusive of vat)	

For invoicing purposes, please provide:	
Sponsor's name	
Contact person	
Address	
Telephone number	
Email Address	

2. List of documentation for approval

PROPOSAL AS APPROVED IN MARCH 2018 FOR ONE YEAR

3. Protocol status (tick ✓)

☐	Open to enrolment
☐✓	Closed to enrolment (tick ✓)
☐	Research-related activities are ongoing
☐	Research-related activities are complete, long-term follow-up only
☐	Research-related activities are complete, data analysis only
☐	Main study is complete but sub-study research-related activities are ongoing
☐	Study is closed → Please submit a Study Closure Form (FHS010)

4. Enrolment

Number of participants enrolled to date	50
Number of participants enrolled, since last HREC Progress report (continuing review)	50

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

Additional number of participants still required	0

5. Refusals

Total number of refusals (participants invited to join the study, but refused to take part)	0

6. Cumulative summary of participants

Total number of participants who provided consent	50
Number of participants determined to be ineligible (i.e. after screening)	0
Number of participants currently active on the study	0
Number of participants completed study (without events leading to withdrawal)	50
Number of participants withdrawn at participants' request (i.e. changed their mind)	0
Number of participants withdrawn by PI due to toxicity or adverse events	0
Number of participants withdrawn by PI for other reasons (e.g. pregnancy, poor compliance)	0
Number of participants lost to follow-up. Please comment below on reasons for loss of follow-up.	0
Number of participants no longer taking part for reasons not listed above. Please provide reasons below:	0

7. Progress of study

Please provide a brief summary of the research to date including the overall progress and the progress since the last annual report as well as any relevant comments/issues you would like to report to the HREC:
The study has been completed as far as gathering of any data from human study subjects is concerned. I failed to notice the expiry date in 30 November 2020 and have just missed the renewal date by 2 days. We need to apply again for an extension, because even though we have completed all the human data collection, the workplace dust analysis was substantially delayed because of laboratory problems. These were just recently received and are being statistically analysed now for final write up.

8. Protocol violations and exceptions (tick ✓ all that apply)

✓☐	No prior violations or exceptions have occurred since the original approval
☐	Prior violations or exceptions have been reported since the last review and have already been acknowledged or approved

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

☐	Unreported minor violations that have occurred since the last review, as well as significant deviations not yet reported are attached for review

9. Amendments (tick ✓ all that apply)

☐✓	No prior amendments have been made since the original approval
☐	Prior amendments have been reported since the last review and have already been approved
☐	New protocol changes/ amendments are requested as part of this continuing review (See note below)

Note: If new protocol changes are being requested in this review, please complete an amendment form (FHS006).
Specific changes in the amended protocol and consent/assent forms must be **bolded**, *italicised* or tracked and all changes must include a rationale.

10. Adverse events

10.1 Please provide below or attach a narrative summary of serious adverse events and/ or unanticipated problems since the last progress report. Please indicate changes made to the protocol and informed consent document(s) as a result (if not already reported to the HREC). Please comment on whether causality to any study procedure or intervention could be established.
None

10.2 Have participants received appropriate treatment/ follow-up/ referral when indicated (e.g. in the case of abnormal or incidental clinical findings, distress or anxiety)?		
☐ Yes	☐ No	✓
If yes, please describe:		

11. Summary of Monitoring and Audit Activities (tick ✓)

11.1 Was this study monitored or audited by an external agency (e.g. SAHPRA, FDA)?		
☐ Yes	☐ No	☐✓ Not applicable

11.2 Did a Data and Safety Monitoring Board publish a report?		
☐ Yes	☐ No	☐✓ Not applicable

11.3 If yes, please identify the agency and attach a summary of the findings.					
Agency Name		Report attached	☐ Yes	☐ No	☐ Not applicable
		DSMB report attached	☐ Yes	☐ No	☐ Not applicable

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

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FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

11.4 Has there been any agency, institutional or other inquiry into non-compliance in this study, or any finding of non-compliance concerning a member of the research team?	
☐ Yes	✓☐ No
If yes, please explain:	

12. Level of risk (tick ✓)

12.1 In light of your experience of this research, please indicate whether the level of risk to participants has:	
☐	Increased
☐	Decreased
☐✓	Shown no change
If there has been a change, please explain:	

12.2 Please provide a narrative summary of recent relevant literature that may have a bearing on the level of risk.
No recent literature on this topic

13. Statement of conflict of interest

Has there been any change in the conflict of interest status of this protocol since the original approval? (tick ✓)	
☐ Yes	☐✓ No
If yes, please explain and if necessary, attach a revised conflict of interest statement (Section #7 in the New Protocol Application Form FHS013):	

14. Signature

My signature certifies that the above is complete and correct.			
Signature of PI		Date	2/12/2020

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

20 Appendix 8: Approval from the Office of the Permanent Secretary for Health, Namibia

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REPUBLIC OF NAMIBIA

Ministry of Health and Social Services

Private Bag 13198 Windhoek Namibia	Ministerial Building Harvey Street Windhoek	Tel: 061 203 2764 Fax: 061 234083
Enquiries: Dr. Ali El Sherif	**Ref:** 8/13/1	**Date:** 17 January 2018

OFFICE OF THE PERMANENT SECRETARY

Mr. Zebra Kasete
Vice President and Managing Director
Dundee Precious Metal Tsumeb
Tsumeb
Namibia

Attention: Ms. Benedicta Uris
Director: Health, Safety & Environment

Dear Sir/ Madam

Re: Permission to Conduct a Study to Characterize the Arsenic Rash at the Smelter

Your letter dated 4th January 2018 bears reference.

Dundee Precious Metals Tsumeb (DPMT) is a subsidiary of the Canadian based Dundee Precious Metals (Pty) Ltd, which is an international company engaged in the acquisition, exploration, development, mining and processing of precious metals.

A condition known as Arsenic Skin Rash has been described for long time at the smelter. This comprises an itchy stinging skin rash around the area where a respirator is worn, and also occurs in other areas of the body which are exposed. Even though the general control measures in the smelter have improved over the past 3-5 years, the incidents of Arsenic Skin Rash still continue.

Against this back ground information, two investigators from the University of Cape Town (UCT), Emeritus Professor Dr. Jonny Myers and Dr. Greg Kew who is a senior lecturer were assigned by the smelter to conduct a formal study of the Arsenic Skin Rashes.

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"Health for All"

The study will aim to better understand the pathophysiology of the disease, especially as to whether it is an allergic condition or an irritant and to establish the causal factors. It is believed that the outcomes of the study will be of much value in improving the prevention and the treatment of such disease. The key objectives of the study are clearly outlined in the attached proposal for the study.

The study will be independently carried out by the above mentioned Occupational Medical Scientists from the University of Cape Town. The individual results will be kept confidential however, the individual workers who will participate in the study will be provided with detailed feedback of their results. The statistical and the group outputs will be made available to the Smelter management, with recommendations as to how these results may guide to more effective preventive measures and controls.

Furthermore, the Chief Medical Officer of Occupational Health Services at the Ministry of Health and Social Services, Windhoek will be kept updated throughout the study processes and informed of the study's outputs and result.

Against this background information, the Ministry of Health and Social Services is hereby granting permission, to conduct the aforementioned study to characterise the Arsenic Skin Rash at the Copper Smelter in Tsumeb.

The Ministry of Health and Social Services will reserve the right to visit DPMT at any suitable time on adhoc basis if needs be. This is to ensure DPMT compliance with the Regulations Related to Health and Safety of Employees at the Workplace, (Labour Act No.6 of 1992, amended as Labour Act No. 11of 2007).

Yours in health,

MS. PETRONELLA MASABANE
ACTING PERMANENT SECRETARY

PERMANENT SECRETARY
MINISTRY OF HEALTH & SOCIAL SERVICES

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