A Field Guide for Detection, Management and Surveillance of Arsenicosis Cases

Edited by Deoraj Caussy, New Delhi, 2005

WORLD HEALTH ORGANIZATION
Regional Office for South-East Asia

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Preface

Globally, arsenicosis, also referred to as arsenism, is an important non-communicable disease resulting from the ingestion of groundwater containing an unsafe level of arsenic. Groundwater contamination, in excess of the WHO guideline value, has been observed in some countries of the South-East Asia Region. The affected countries are Bangladesh, India, Myanmar, Nepal and Thailand. Over 10 million tubewells are in use in the Region, potentially exposing between 40 and 50 million persons to unsafe levels of arsenic.

To mitigate the health effects of arsenic in the South-East Asia Region, in 2003, WHO prepared this Field Guide for Detection, Management and Surveillance of Arsenicosis Cases. The materials were developed and field-tested in regional and national workshops in Bangladesh, India and Thailand.

This guide is primarily for human resource development in the area of arsenic mitigation in the Region.

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Section 1. Introduction

1.01 BACKGROUND AND PURPOSE OF THE MODULE

Drinking water contaminated with an unsafe level of arsenic is known to result in adverse health outcomes. In many parts of the world, the source of drinking water is groundwater. While groundwater is relatively safe as regards bacterial contamination and other impurities, it is prone to chemical contamination such as arsenic. Arsenic contamination of groundwater may occur in two ways: drawing of water from aquifers that naturally contain arsenic or contamination from anthropogenic activities such as mining. Groundwater contamination in excess of the World Health Organization guideline value of 0.01 mg/L has been observed in parts of USA, Canada, Argentina, Chile, Mexico, Hungary and many countries of the South-East Asia Region. The most affected countries in the South-East Asia Region are in the river basins of the Ganga-Brahmaputra or the Mekong Delta. Affected countries include India, Bangladesh, Nepal, Myanmar, Vietnam, Cambodia, Laos and China.

Until now there have been no internationally accepted criteria for the diagnosis and management of arsenicosis or diseases associated with arsenic exposure. The purpose of this document is to serve as a guideline for the diagnosis, surveillance and management of arsenicosis. It is recognized that arsenicosis may manifest with or without skin manifestation. However, generally skin manifestation is the primary condition leading a patient to seek medical care. Therefore, the emphasis in this document is the diagnosis of arsenicosis based on dermal manifestations.

The use of this document will ensure consistency in the diagnosis and management of arsenicosis cases, training of health workers and provide a set of objective criteria for the evaluation of any intervention measures. The ultimate aims are to set the norm, standards and guidelines for a harmonized protocol on case detection, management and surveillance. These criteria were developed by an expert group working in the field of arsenic taking into account the best available evidence for action that is currently available. It is envisaged that national authorities, sister agencies and development partners will use this document to manage arsenic

contamination in their respective countries and may further translate it into the local language.

1.2 ROLE OF WHO IN ARSENIC MITIGATION

WHO first assessed the risk of arsenic in drinking water in 1958 by producing the International Standards for Drinking Water. In 1981, in collaboration with other UN agencies, WHO published the "Environmental Health Criteria on Arsenic" to evaluate the health risks to humans from exposure to arsenic. The Environmental Health Criteria on arsenic was updated in 2001. Globally, the WHO Guidelines for Drinking Water Quality, published in 1993, have been used as the basis for the development of national standards for arsenic.

Realizing the serious health impact of arsenic contamination in the South-East Asia Region of WHO, the Regional Office for South-East Asia, since 1996, has provided policy and technical support to national governments of the affected countries. In 1997, the Regional Office held a regional consultation of experts and made 20 key recommendations for arsenic mitigation. These recommendations have been used as the basis for designing projects and implementing programmes by national governments, donor agencies and NGOs alike. However, on reviewing the progress of implementation, it was evident that critical gaps in case reporting and case management remained to be remedied. In 2002, the Regional Office launched an arsenic mitigation initiative which was founded on policy support stemming from the recommendations of the High-Level Task Force, the Regional Committee and the Advisory Committee on Health Research.

1.3 PROGRAMME STRATEGY

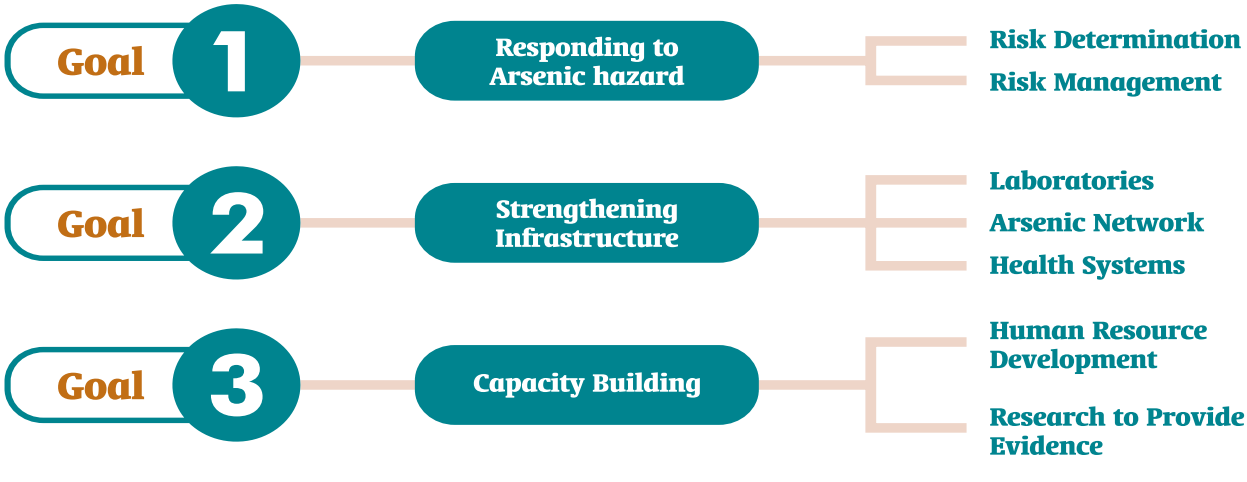
The programme strategy focuses on WHO's normative role in applying the health risk assessment paradigm for the mitigation of the health impact of arsenic exposure. As shown in *Figure 1*, the arsenic mitigation initiative is implemented through a strategic plan focusing on three main goals, namely:

(1) responding to arsenic hazard through consistent application of health risk paradigm of exposure assessment, risk characterization and risk management,

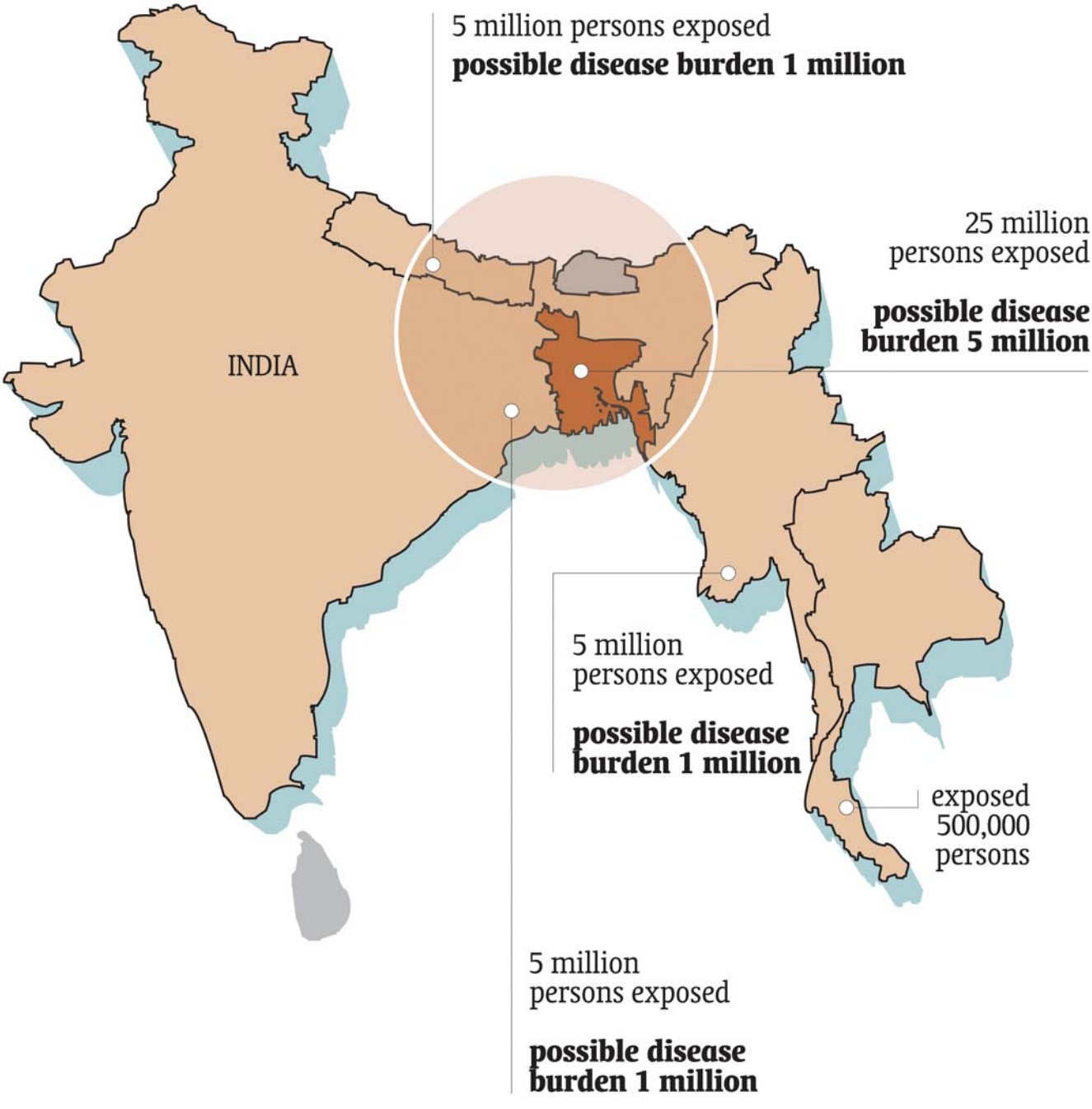
(2) strengthening infrastructure for arsenic mitigation through promotion of a network of centres of excellence, and

(3) building capacity through human resource development.

Figure 1
STRATEGIC GOALS FOR ARSENIC MITIGATION



Section 2. Epidemiology of Arsenicosis in S-E Asia



The South-East Asia Region contains a natural arsenic-rich eco-belt formed by arsenic-laden alluvium or sediments deposited in the Brahmaputra-Gangetic river basins millions of years ago. Countries of South-East Asia that are in this belt include Bangladesh, parts of India, Myanmar and Nepal. Anthropogenic mining activities in one province of Thailand have also been responsible for arsenic contamination. Groundwater from tubewells is a predominant source of drinking water in many of the Member Countries in which contamination of groundwater often exceeds either the WHO guideline values or the respective prevailing national standards. It is estimated that some 30 million persons may be at risk for arsenic-related diseases by virtue of consuming arsenic contaminated water in the region.

2.01 FORMS AND OCCURRENCE OF ARSENIC

Arsenic is an element that can combine with both metals and non-metals to form inorganic and organic compounds. The inorganic forms are toxic to human health and consist mostly of arsenite and arsenate compounds. The organic forms are comparatively non-toxic and are mostly present in sea foods.

2.02 PATHWAY FOR EXPOSURE

Humans may be exposed to inorganic arsenic from all four environmental matrices of air, water, food and soil. General environmental exposures include ingestion of soil by children, ingestion of certain traditional medicines and various food items and ingestion of water. Arsenic is present at levels ranging from 0.2 to 40 μg/g of soil while in urban air the concentration of arsenic is at levels around 0.02 μg/m^3 of air. The levels of arsenic in food items in the affected countries vary but they currently pose a lesser threat than drinking water.

2.03 HEALTH IMPACT OF EXPOSURE

The health impact of exposure to arsenic depends on the dose, the modality and duration of exposure as well as the source and type of arsenic. Prolonged exposure to non-lethal doses of 0.005 to 0.09-mg/kg-body weight/day results in arsenicosis, a disease that is characterized by dermatological features of pigmentation and keratosis. Arsenicosis is also called arsenicism, and is also referred to as black foot disease, black skin fever etc. in various parts of the world. Cancers of the lungs, bladder, kidney and skin have been consistently observed in subjects drinking arsenic-contaminated water. Presently, inconclusive evidence exists for linking arsenic to cardiovascular disease, diabetes or negative reproductive health outcomes.

Section 3. Clinical Aspects

3.01 PATHOGENESIS

Both organic and inorganic arsenic are absorbed from the gastrointestinal tract; however, arsenic toxicity results from absorption of trivalent and pentavalent inorganic arsenic.

After absorption, arsenic is cleared rapidly from the blood and during its "first-pass" phase it reaches the liver where it is detoxified by conversion into MMA and DMA. Arsenic metabolism is characterized by two sequential reactions:

(a) First, the reduction of pentavalent arsenic to trivalent arsenic in the presence of gluthathione,

(b) The second is oxidative methylation reaction in which the trivalent forms of arsenic are sequentially methylated to form mono, di and trimethylated products using s-adenosyl methionine (SAM) as methyl donor and GSH as an essential co-factor. Arsenic methylation occurs primarily in the liver.

Urine is the primary route for elimination of both pentavalent and trivalent inorganic arsenicals, 45-75% of the administered dose being excreted in the urine within a few days to a week. Arsenate can uncouple oxidative phosphorylation in mitochondria by substituting for inorganic phosphate in the synthesis of ATP, the main energy source of cellular metabolism. Arsenite reacts readily with vicinal sulphydryl groups of many essential enzymes and proteins within the cell. It is the affinity of arsenite for the sulphydryl group that accounts for its accumulation in keratin-rich tissues such as skin, hair and nails.

Chronic arsenic toxicity produces various dermal and systemic manifestations including cancer. Trivalent arsenic is believed to be a carcinogen that induces chromosomal abnormalities including changes in the structure and number of chromosomes and sister chromatid exchanges. The exact molecular mechanism of arsenic induced carcinogenesis is less understood.

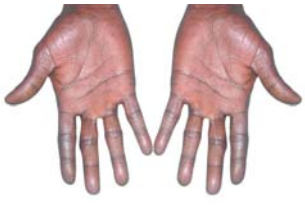
3.02 SKIN MANIFESTATIONS OF CHRONIC ARSENIC INGESTION

The skin manifestations of chronic arsenicosis, resulting from ingestion of arsenic, can be either non-malignant or malignant. The hallmarks of non-malignant manifestations are dermal changes concomitantly characterized by increased pigmentation and hardening of the skin, that is a combination of melanosis and keratosis. The characteristic cutaneous lesions of arsenicosis are illustrated in *Table 1*. The most common sequence is the gradual development of spotted or "raindrop pigmentation", followed by the gradual emergence of hyper-keratotic changes. Both conditions take several years ranging from 6 to 9 years depending on the exposure dose and other host factors.

The hyper-pigmentation commonly appears in a finely freckled, "raindrop" pattern that is particularly pronounced on the trunk and extremities and is symmetrically distributed bilaterally. Mucous membranes such as the undersurface of tongue or buccal mucosa may also be involved. Other patterns

Table 1
CHARACTERISTIC CUTANEOUS LESION OF ARSENICOSIS

MELANOSES



MELANOSIS
Palm of a man suffering from melanosis

Fine-freckled or spotted pattern on trunk and extremities (rain-drop pigmentation)

Diffused or generalized hyper pigmentation

Rounded hypo-pigmented or de-pigmented macules on a normal or hyper-pigmented background (leukomelanosis)

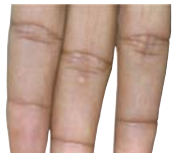
Localized or patchy pigmentation generally on the body

Pigmentation of mucous membranes (e.g. oral mucosa), usually in combination with other changes listed above (less common)

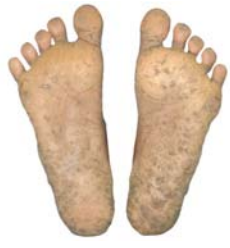
KERATOSES

Characterized by thickening of the skin and appearance of papules or nodules that can both be further sub-categorized as follows:

MILD
Slight thickening, or minute papules (less than 2 mm) of palms and soles, often associated with a grit-like texture, that may be primarily detectable by palpation



MODERATE
Multiple, raised keratosis (>2 to 5 mm), appearing



include diffused hyper-pigmentation (melanosis); localized or patchy pigmentation and so-called leukodermia or leukomelanosis in which the hypo-pigmented macules take a spotty, white appearance.

Arsenical hyper-keratosis predominantly appears on palms and the plantar aspect of the feet, although involvement of the dorsum of the extremities and trunk has also been described. In the early stages, the involved skin might have an indurated, grit-like character that can be best appreciated by palpation; however, the lesions usually advance to form raised, punctuated, 2-4 mm wart-like keratosis that are readily visible. Occasional lesions might be larger (approximately 1 cm) and have a nodular or horny appearance. In severe cases, the hands and soles present with diffused verrucous lesions. Cracks and fissures may be severe in the soles.

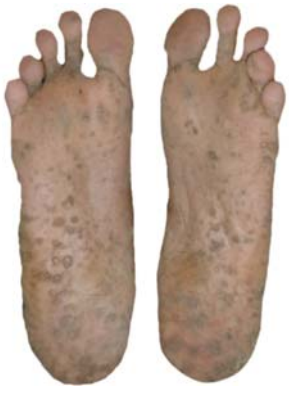
The most common type of malignancy following chronic exposure are skin cancer such as Bowen's disease, squamous cell carcinomas or basal cell carcinomas, although internal malignancies are probably related as well.

mainly or exclusively in a symmetric distribution on palms and soles

SEVERE

Large discrete or confluent keratotic elevations (> 5 mm) on palms and soles, with nodular, wart-like or horny appearance.

Less commonly, there may also be involvement of the dorsum of the extremities, and trunk. Diffused thickening of the palms and soles may occur alone or in combination with the keratotic nodules.



KERATOSIS

Mostly characterized by thickening of palms and soles, alone or in combination with nodules

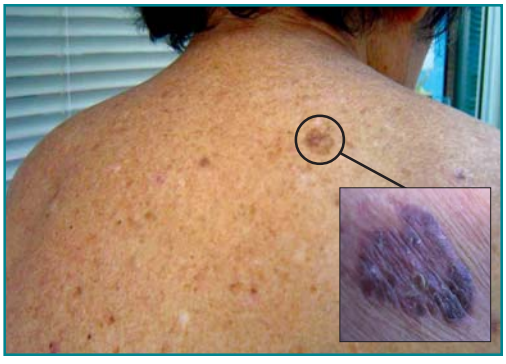
BOWEN'S DISEASE

In situ squamous cell carcinoma / intra-epidermal carcinoma

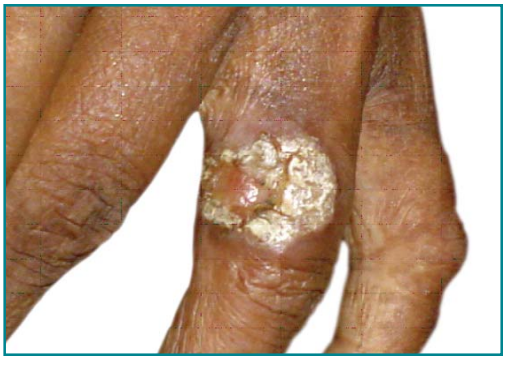
May appear as multiple macules, papule, or plaque (1mm to many cm) in non-sun exposed areas. Usually a scaly, crusted erythematous plaque. They are usually sharply demarcated and seldom indurated *(pic overleaf)*. If the crust is removed, the underlying surface may be red and oozing.

SQUAMOUS CELL & BASAL CELL CARCINOMA

Both these cancers have highly variable clinical appearances, depending in part on the stage of the malignancy. Squamous Cell Carcinoma is characterized by ulcerated or fungating growth *(pic overleaf)*. Basal cell carcinoma is initially characterized by pearly translucent nodules leading to ulcerations.



BOWEN'S DISEASE
In situ squamous cell carcinoma / intra-epidermal carcinoma seen here as a sharply demarcated plaque.



SQUAMOUS CELL CARCINOMA
Ulcerated growth, peculiar to the condition, seen on the finger of a patient.

*Bowen's disease, or in situ squamous cell carcinoma / intra-epidermal carcinoma m*ay appear as multiple macules, papule, or plaque (1mm to many cm) in non-sun exposed areas. It usually presents as a scaly, crusted erythematous plaque that are sharply demarcated and seldom indurated.

Squamous cell and basal cell carcinoma have highly variable clinical appearances, depending in part on the stage of the malignancy. Squamous Cell Carcinoma is characterized by ulcerated or fungating growth. Basal cell carcinoma is initially characterized by pearly translucent nodules leading to ulcerations.

3.03 DIFFERENTIAL DERMAL DIAGNOSIS

The classic pattern of rain-drop pigmentation is relatively specific for arsenic, and its occurrence together with palmar-plantar hyperkeratosis is pathognomonic for arsenicosis. Nonetheless, some of the skin changes associated with arsenic may appear the same or similar to those encountered in other medical conditions. *Table 2* lists at least five categories of dermal manifestations mimicking arsenical dermatosis and include diffused melanosis, spotted melanosis, leukomelanosis, diffused keratosis, and nodular keratosis. Clinicians and paramedical personnel practising in primary care settings can be trained to screen patients for the possible presence of characteristic arsenic-related skin lesions, but a differential diagnosis examination using the criteria of *Section 9* by an experienced dermatologist or other physician with relevant expertise is recommended for confirmation of the diagnosis.

3.04 OTHER NON-DERMAL MANIFESTATIONS OF CHRONIC ARSENICOSIS

The most common systemic manifestations include neurological, haematological, gastrointestinal and respiratory complications.

Complications of the central and peripheral nervous systems are neuropathy characterized by paresthesias and numbness. Studies from Taiwan have documented the presence of black-foot disease, a unique peripheral arterial disease characterized by severe systemic arteriosclerosis as well as dry gangrene and spontaneous amputations of affected extremities at end stages. Though the incidence of leg pain or intermittent cramp in the leg muscles is not uncommon, dry gangrene is less frequently seen in the Indo-Gangetic Basin.

Haematological complications include leukopenia, anaemia and spleenomegaly.

Gastrointestinal complications include symptoms like anorexia, vague abdominal pain or chronic diarrhoea; liver enlargement with or without non-cirrhotic portal fibrosis are also seen.

Respiratory complications include chronic cough or bronchitis.

Section 4. Case Definitions

4.01 DEFINITION

Arsenicosis is defined as a chronic health condition arising from prolonged ingestion of arsenic above the safe dose for at least six months, usually manifested by characteristic skin lesions of melanosis and keratosis, ocurring alone or in combination, with or without the involvement of internal organs.

4.02 RATIONALE FOR CASE DEFINITION

The accurate detection of arsenic cases is the cornerstone for case management and reporting. In disease surveillance, a case is usually defined by clinical signs, symptoms, or laboratory measures. In applying this approach for arsenic case definition, two practical difficulties arise. First, there are several skin conditions in South-East Asia that share major features with arsenic-defining conditions and, secondly, the use of laboratory measures is not uniformly available under all local conditions. Therefore, the selection of case definition for arsenicosis ultimately depends on the objective of the public health programme. The present objectives in formulating a case definition are to:

(a) achieve consistent case detection and reporting in the Region,

(b) provide an objective way to evaluate the efficacy and effectiveness of any interventions,

(c) attain consistency in the training of health care workers in the Region, and

(d) enable valid comparison of studies.

4.03 CRITERIA FOR CASE DEFINITION

In formulating a working case definition, it is generally prudent not to include any clinical information or diagnostic test which might not be uniformly available under conditions of local medical practice. The case criteria should be appropriate for the diagnostic resources available to the community where the problem exists. However, this may make the case definition less precise. Therefore, a balance between scientific precision and field practicality has been maintained in devising an algorithm whereby a case can be either clinically confirmed only or clinically and laboratory confirmed depending on the availability of resources or clinical expertise or the purpose for which the case definition is needed. Thus, the recommended case definition algorithm uses two major diagnostic criteria, namely:

(a) the presence of pigmentary and keratotic skin lesions, and

(b) evidence of exposure to elevated levels of arsenic established by history of intake of arsenic contaminated water, or by arsenic concentration in hair or nails.

4.04 CLINICAL CRITERIA

The first diagnostic criterion requires the presence on physical examination of any of the pigmentary or keratotic skin signs listed in *Table 1*. These signs encompass a spectrum of non-cancerous and cancer cutaneous findings that are well-recognized features of chronic arsenic ingestion.

4.05 LABORATORY CRITERIA

A reliable history of consuming drinking water with an elevated concentration of arsenic for at least six months is sufficient to establish exposure. *See Box 1*. In the absence of adequate information regarding a subject's exposure history, the finding of elevated levels of arsenic in a subject's hair or nails could offer presumptive evidence of elevated arsenic exposure. Arsenic testing should be conducted using standardized sample collection methods and acceptable laboratory techniques as elaborated in *Section 5*.

4.06 ALGORITHM

A diagnostic algorithm for case detection provides a simplified scheme for implementing the case definition and classifying patients under field conditions and in various levels of health care facilities. The suggested algorithm is shown in *Flowchart 1*.

4.07 SUSPECTED CASE

A "suspected case" is a subject who shows characteristic skin lesions or pigmentary changes or keratosis on first presentation and who has not undergone in-depth medical examination or laboratory testing. The list of skin lesions for suspecting a case is detailed in *Table 1*.

The classification of "suspected case" is temporary. It should be reclassified as "probable", "confirmed" or "non-arsenic" after further clinical examination and or laboratory testing.

4.08 PROBABLE CASE

A "probable case" is a suspected case that has undergone further clinical examination and belongs to one of the two categories as below:

EITHER
(a) a suspected case showing melanosis AND bilateral keratosis involving palms and soles

OR
(b) a suspected case showing unilateral melanosis or keratosis after excluding other skin lesions mimicking arsenicosis.

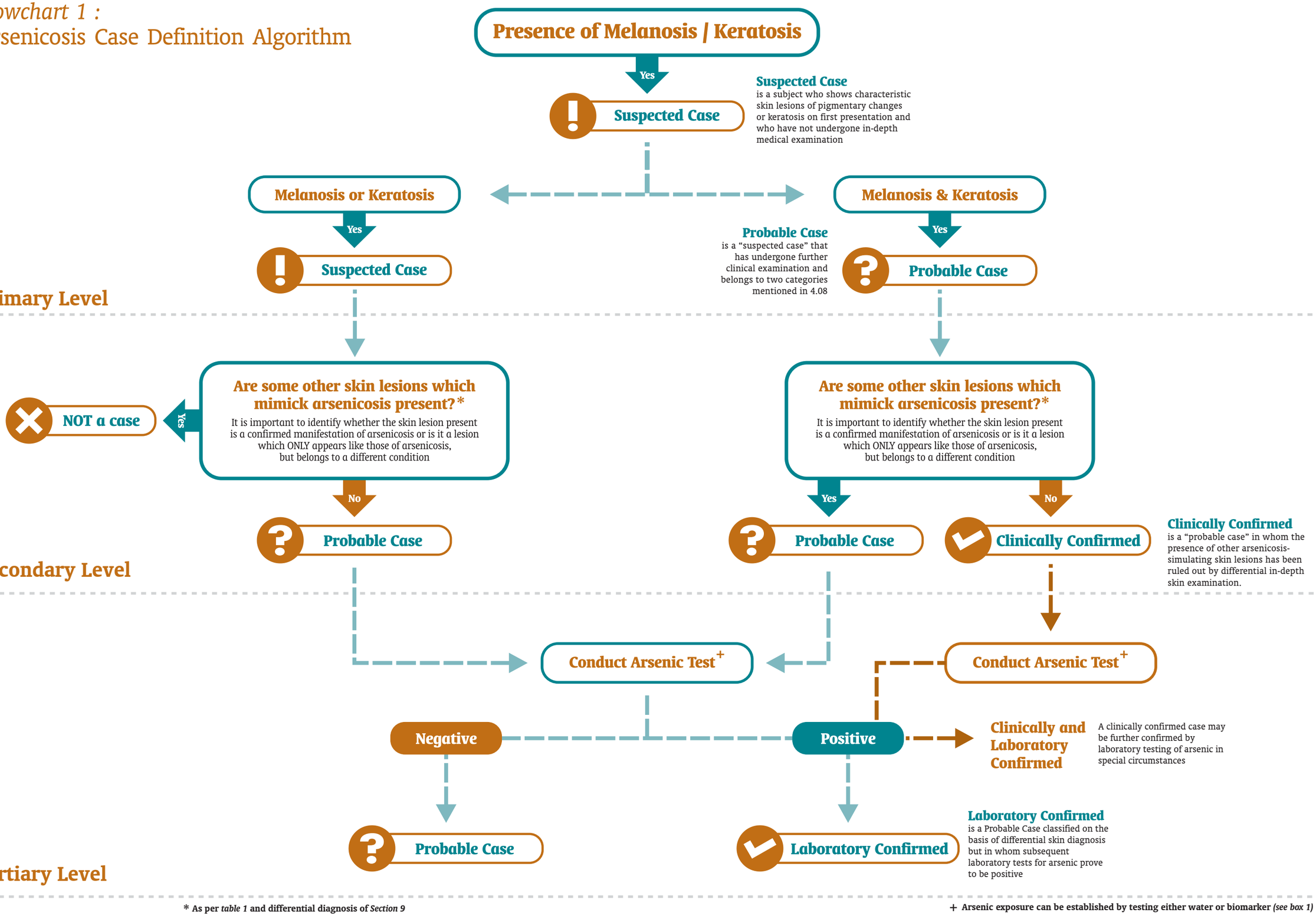
Probable cases whose arsenic tests are subsequently found to be negative maintain the status of probable case.

4.09 CLINICALLY CONFIRMED CASE

A "clinically confirmed case" is a "probable case" in whom the presence of other arsenicosis-simulating skin lesions has been ruled out by differential in-depth skin examination by either a trained dermatologist or an arsenic expert. The differential features to be used are given in *Table 2* and further elaborated in *Section 9*.

< flip for gatefold: Flowchart 1

Flowchart 1 :
Arsenicosis Case Definition Algorithm



* As per *table 1* and differential diagnosis of *Section 9*

\+ Arsenic exposure can be established by testing either water or biomarker *(see box 1)*

Table 2

COMMON CONDITIONS TO BE CONSIDERED FOR DIFFERENTIAL DIAGNOSIS OF NON-CANCER SKIN LESIONS

CATEGORY	MAJOR CONDITIONS FOR CONSIDERATION	DISTINGUISHING FEATURES
Diffused Melanosis	Actinic dermatosis	Found on exposed part of the body
	Melasma	Found mainly on face
	Ashy dermatosis	Diffused pigmented macules mainly on trunk
Spotted Melanosis	Pityriasis versicolor	Hyperpigmented macules with fine scale on trunk, face and neck extremities.
	Freckle	Mottled pigmentation on face and trunk increases with sun exposure.
	Lichen planus	Starts with violaceous pruritic papular lesion on trunk and extremities and produces spotty pigmentation on resolution.
Leuco-Melanosis	Idiopathic guttate hypomelanosis	Multiple depigmented macules on trunk and extremities.
	Pityriasis versicolor	Hyper and hypo-pigmented macules with scales on trunk, face, neck and extremities.
	Pityriasis – lichenoides chronica	Erythematous papular lesion followed by hypo-pigmented macules
	Leprosy	Macular hypo-pigmented or erythematous lesions, usually with loss of sensation. There may be involvement of peripheral nerves which are usually thickened and tender.
Diffused Keratosis	Psoriasis (palms and soles)	Diffused keratoderma on palms and soles, with or without scaly psoriatic patches on the other sites.
	Eczema	Lichenified lesions with pruritus and occasional oozing.
	Occupational keratosis	Keratotic lesions corresponding to site of friction.
	Tinea pedis	Scaly fissured keratotic lesion, with or without fissures on webs.
	Pitted keratolysis	Multiple pitted (depressed) and keratotic lesions on soles.
Nodular Keratosis	Occupational keratosis	Same as above.
	Verruca vulgaris	Multiple verrucous pigmented papules and nodules on trunk, extremities and dorsum of hands and feet.
	Corns/calluses	Localized keratotic lesions at the site of friction.
	Seborrheic keratosis	Discrete well-defined pigmented papules and plaques on sun-exposed areas.

4.10 LABORATORY CONFIRMED CASE

A probable case classified on the basis of differential skin diagnosis becomes a "laboratory confirmed case" when subsequent laboratory tests for arsenic prove to be positive.

4.11 CLINICALLY AND LABORATORY CONFIRMED CASE

A "clinically and laboratory confirmed case" is a "clinically confirmed case" in whom the arsenic test is also positive by the criteria recommended in *Box 1*.

4.12 NON-ARSENIC CASE

A "non-arsenic case" is a "suspected" or "probable" case in which the medical specialist finds that the patient's skin condition is due to a cause other than arsenic exposure.

4.13 SENSITIVITY AND SPECIFICITY OF CASE DEFINITION

The rigor and complexity of a case definition and its sensitivity and specificity vary depending on the purpose for which the definition will be applied. In clinical settings, it is appropriate to use a broader and simpler case definition that will apply to capture all possible spectrums of clinical presentations. The present case definition algorithm for non-cancerous skin lesions shows acceptable sensitivity (>80%) and specificity (>80%) for the prevalent arsenic-associated skin lesions.

It must be remembered that all arsenicosis cases may not necessarily show dermal manifestations at the outset. Hence those cases will not be captured by the present algorithm. However, clinical evaluation for management of suspected cases described in Section 6 will pick up such cases that will have to be appropriately followed up medically.

4.14 ROLE OF NATIONAL EXPERT COMMITTEE

There may be instances where the application of the present algorithm does not lend itself to some clinical cases. In such cases it is advisable to refer these types of cases to a nationally constituted expert committee for advice. If such a committee does not exist in a particular country, then referral for advice from a regional centre of expertise is recommended.

Section 5. Laboratory Support

Box 1
LABORATORY CRITERIA FOR ESTABLISHING EXPOSURE HISTORY OF ARSENICOSIS CASES

TESTING WATER

Consumption of drinking water with an arsenic concentration in excess of prevailing national standards for at least six months.

TESTING BIOMARKER

If data on the arsenic concentration of previously consumed water is unavailable, an elevated concentration of arsenic in hair (> 1 mg/Kg of hair) or in nail clippings (> 1.5 mg/Kg of hair) may serve as presumptive evidence of elevated arsenic exposure.

THE ARSENIC CONCENTRATION should be determined using a validated method performed by trained personnel in a laboratory meeting national standards and practising standard operating procedures.

Laboratory support provides ancillary information in instances where probable cases cannot be clinically confirmed or in instances or countries where a laboratory diagnosis is required for final confirmation.

5.01 TYPES OF SPECIMEN

WATER: Arsenic exposure can be established by testing the water that is currently being consumed.

HAIR AND NAIL: Hair or nails provide circumstantial evidence for history of past exposure within the preceding nine months.

URINE: Both organic and inorganic forms of arsenic are excreted in the urine which will test positive for arsenic. Thus, recent exposure to arsenic can be established from urine samples provided the subjects have not been consuming sea-food in the preceding four days. Alternatively, the chemical form of arsenic must be differentiated by laboratory methods.

BLOOD: Blood is of no value in establishing chronic arsenic exposure because of the short half-life of arsenic in blood.

5.02 COLLECTION, STORAGE AND SHIPMENT

WATER AND URINE: For water and urine samples it is advisable to collect 50 ml of samples. Care must be taken to avoid contamination and prevent speciation changes during sample collection and storage. Plastic containers should be acid washed and traces of oxidizing agents avoided to preserve the oxidation state of the arsenic compounds, in instances where speciation is required. The container should also be completely filled to prevent oxidation from the air in the bottle.

Concentrated hydrochloric acid (1 ml of acid to 100 ml of urine) can be used to prevent bacterial growth for urine samples. The samples are stable at room temperature for at least a week and at –20°C for 6 months. For longer periods it is recommended that the samples be frozen at –80°C.

Urine and water samples can be shipped at room temperature. Avoid shipment before a weekend or holidays. All specimens must be accompanied by a duly filled request form containing information on the patient's name, referring doctor, clinical diagnosis and an address for sending results. The request form should be packed in a separate plastic bag for protection in the event of specimen leakage.

HAIR AND NAILS: Care should be taken to avoid superficial arsenic contamination. The hair must be washed with arsenic-free shampoo and also be free of colouring chemicals containing arsenic. For a female subject, collect 30 hairs 6 cm. long from the base of the hair, discard the hair beyond 6 cm. For males, collect 60 short hairs from the base. For nails, let them grow for one month then clip every finger and toe nail—this represents 9 months of exposure.

Specimens of hair and nails can be stored at 4°C until tested. Prolonged storage may lead to endogenous fungal growth in some instances. Hair and nails can be shipped at room temperature.

5.03 ANALYTICAL PROCEDURES

Historically, colorimetric and gravimetric methods have been used for determining arsenic. However, these methods are either semi-quantitative or lack sensitivity. In recent years, the technique of atomic absorption spectrometry (AAS) has become the method of choice due to its selectivity and sensitivity in the detection of arsenic. Thus, AAS may be considered as the standard reference method ("gold standard") for the evaluation of other test methods. A commonly-used variant of the AAS technique is the highly sensitive hydride generation atomic absorption spectrometric method (HGAAS).

For mass screening under field conditions, or in a situation where no laboratory facilities exist, it is often practical to use a reliable test-kit for testing arsenic. A number of such test kits are commercially available. However, the validity of these kits in comparison to other test methods must be established. It is also recommended that Member Countries develop policy and guidelines for the selection, import and use of these kits in consultation with their respective national control authorities (NCA).

Before using a test kit, all instructions and material safety data sheet must be read and understood. The persons performing the analysis must also be trained in a laboratory which meets national standards and practices standard operating procedures. The range and limitations of the kit must be established. Chemicals such as sulfite and selenium or other impurities can interfere with the performance of some kits and these must be established for each instance.

5.04 QUALITY CONTROL

Testing of arsenic should be undertaken by laboratories that have been nationally recognized and in which appropriate quality control measures are routinely performed. Such laboratories should incorporate both internal and external quality controls and follow accepted Standard Operating Procedures (SOP). The person performing the testing must also be appropriately trained in this area. It is advisable for national authorities to have policy and guidelines on the introduction and use of SOP in laboratories performing arsenic testing, including the use of kits and also to maintain a list of laboratories meeting these standards.

5.05 INTERPRETATION OF LABORATORY RESULTS

WATER: The current WHO guideline value of arsenic in water is 0.01 mg/L (or 10 μg/L also expressed as 10 part per billion (ppb). Thus, any sample containing arsenic concentration of greater than 10 μg/litre is considered positive. Some countries may have national standards of arsenic that are 50 μg/litre. In such instances arsenic concentration in excess of 50 μg/litre is considered positive.

URINE: A urine sample showing more than 50 μg/litre may be taken as evidence of recent exposure provided the subject has not consumed sea food during the previous four days.

HAIR AND NAILS: The value in hair and nails is not known with certainty. On review of the literature it can be assumed that arsenic concentration of greater than 1 mg/kg of dry hair and arsenic concentration of more than 1.5 mg/kg of nail may be considered as indicative of exposure to an unsafe dose of arsenic within the preceding 11 months.

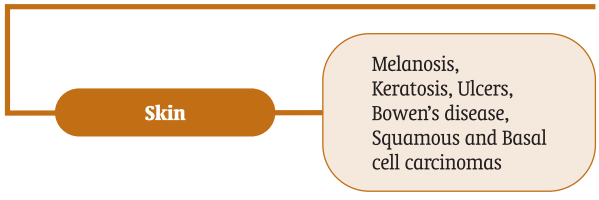
5.06 LABORATORY NETWORK

In many countries there is a network of laboratories that can perform tests to detect arsenic. Usually, testing of water is the responsibility of the Public Health Engineering Department or appropriate water authorities of the respective countries. In many countries, testing can also be done by institutions, universities or private laboratories. However, only specialized laboratories can distinguish the chemical form or species of arsenic. For a list of reliable laboratories in your country, consult your national authorities. In countries where such facilities do not exist, it is suggested that specimens be tested in a reference laboratory in the Region.

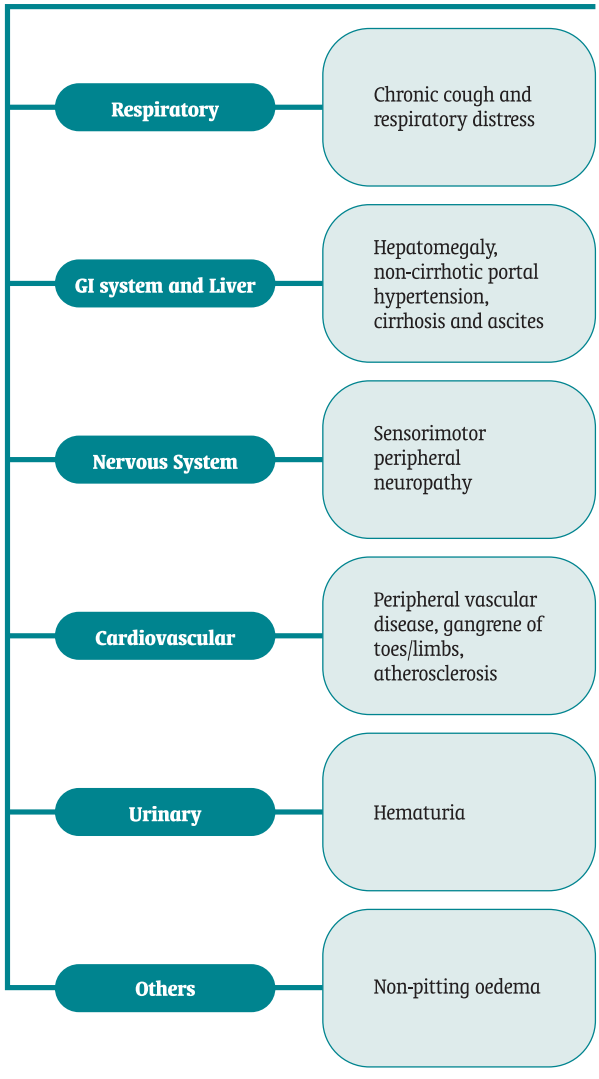
Section 6. Case Management

Table 3
CHECKLIST OF SUGGESTED CASE MANAGEMENT FOR SYSTEMIC MANIFESTATION OF ARSENICOSIS

Dermatological Manifestations



Non-Dermatological Manifestations



6.01 BASIC PRINCIPLES FOR MANAGEMENT

Drugs used in the management of arsenicosis should be ideally based on solid evidence generated through randomized controlled clinical trials. However, more often, recommendations have to be made without such evidence. In those circumstances it is a mixture of less than adequate evidence and the consensus of experts in the area. The management of arsenicosis falls into this category.

Management approaches for arsenicosis utilized in the Region to-date have included the use of many drugs, agents and nutrients. Therefore, therapies that have not been validated in arsenicosis through randomized double-blinded controlled clinical trials, or have not been part of standard medical treatment, cannot be recommended at this point.

6.02 AVAILABLE MANAGEMENT STRATEGIES

Future studies will inevitably bring about major changes in management. Presently, the management of arsenicosis focuses on five key approaches:

(1) Cessation of exposure to drinking water or other items with elevated concentration of arsenic;

(2) Administration of drugs or nutrients directed at hastening recovery or averting disease progression;

(3) Provision of non-specific supportive care to improve physical symptoms or treat selected complications;

(4) Secondary prevention of latent effects through medical surveillance, and

(5) Counselling and education to address psychosocial sequelae of the illness and provision of appropriate rehabilitation.

6.02.1 CESSATION OF EXPOSURE TO DRINKING WATER

As there is no known specific treatment for arsenicosis, the prudent intervention is to stop consumption of arsenic-contaminated water. Appropriate counselling for safe water options and health consequences of consuming arsenic-contaminated water should be supported through standard Information, Education and Communication (IEC) strategies. In general, the water supply option for an area will depend on the availability, quality and development potentials of available alternative water sources in a given area. A single option may not be suitable or affordable for people with different social and economic conditions. Some of the main strategies for safe water should include:

(1) T*reatment of surface water*. Treatment of surface water can be an option in areas with perennial surface water of adequate quantity and good quality. Some of the options include slow sand filters or pond sand filters; pressure filtration followed by disinfection; small-scale conventional or prototype treatment plants, and conventional surface water treatment plants.

(2) *Rainwater harvesting*. Rainwater harvesting has good potential for safe water supply in most parts where there is rainfall. It can be combined with household-based technology with provision for adequate storage tanks. This method is particularly useful in areas where adequate quantity and good quality of surface water sources are limited.

(3) *Deep tubewell*. In some areas, deep tubewells can provide water of acceptable quality. Before boring a deep tubewell it is important to ensure that the deep aquifers are separated from the shallow contaminated aquifers by relatively impermeable layers. The quality of the water must be monitored for arsenic and other heavy metals that pose health risks.

(4) *Treatment of arsenic contaminated water*. In some areas, the only available option may be to treat the arsenic contaminated water. A variety of options are available depending on technologies, cost and acceptability and range from filter units for domestic use, through filter units for community level use to piped supply of arsenic treated-water.

6.02.2 ADMINISTRATION OF NUTRITIONAL SUPPLEMENTS

Administration of non-specific nutritional supplements or anti-oxidants directed at hastening recovery or averting disease progression has been undertaken in many countries. Some commonly used anti-oxidants include beta carotene, vitamin E and vitamin C. Presently, there is no large-scale randomized-controlled double-blinded trial to evaluate the efficacy of these treatment regimens. Their use depends on the national policy and the recommendations of the concerned medical bodies in respective countries.

6.02.3 PROVISION OF NON-SPECIFIC THERAPY

Symptomatic treatment for patients with keratosis or keratosis and melanosis includes the application of keratolytic agents. Presently, 5-10% of salicylic acid and 10-20% of urea-based ointment for the treatment of keratotic lesions is the most common prevailing practice, as evidenced by literature review. Higher doses need further evaluation.

6.02.4 SECONDARY PREVENTION OF LATENT EFFECTS

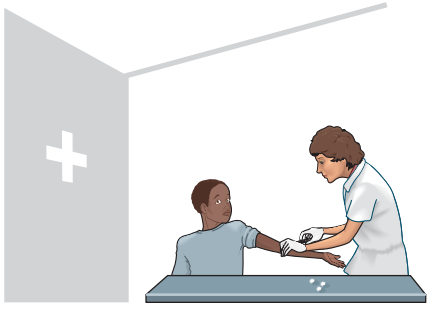
Secondary prevention of latent effects should be done through medical surveillance. The management of arsenic-associated cancer patients should follow the prevailing national standards and practice for the management of cancer patients in general.

6.02.5 COUNSELLING AND EDUCATION

Counselling and education address the psychosocial sequelae of the illness and provide appropriate

Flowchart 2

MANAGEMENT OF ARSENICOSIS CASES AT VARIOUS LEVELS OF HEALTH SERVICES



Primary Health Care Services

For instance, PHC etc.

HISTORY and physical examination for detection of arsenicosis.

TREATMENT of symptoms of systemic manifestations listed in Table 3.

COUNSELLING to stop consumption of arsenic-contaminated water, and provision of information on arsenic-safe water supplies.

ADVICE on adequate nutrition

PROVISION of supportive care by topical keratolytic agents for patients with keratosis. Presently 5-10% of salicylic acid and 10-20% of urea based ointment is used.

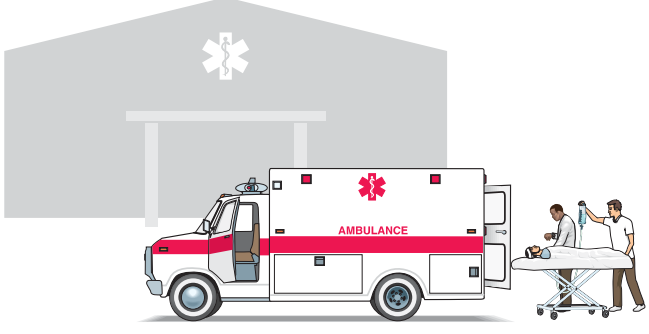
SURVEILLANCE of arsenicosis patients on a periodic basis

EDUCATION of patients and community: counseling for recognition and management of systemic manifestation of arsenicosis

FOLLOW-UP of cases and referral to higher levels as indicated

REHABILITATION services to be arranged

RECORD keeping and reporting.



Secondary Health Care Services

District Hospitals etc.

CONFIRMATION of diagnosis according to standard criteria based on the case-classification algorithm

MANAGEMENT of Bowen's disease and skin cancer. Management of systemic disorders.

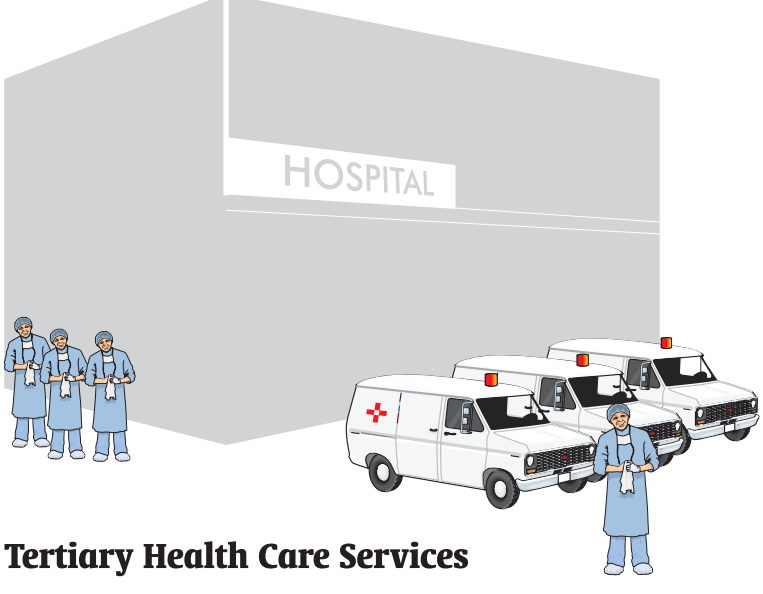
MONITORING of biological and water samples as needed

REFERRAL of complications

REHABILITATION services to be provided.

RECORD keeping and reporting of cases.

TRAINING and support for primary health care providers



Tertiary Health Care Services

State Hospitals etc.

MANAGEMENT of skin and other cancers

MANAGEMENT OF OTHER systemic complications listed in Table 3

REHABILITATION services to be provided

RESEARCH on case management including epidemiology, natural history and therapeutic regimens and interventions

TRAINING of trainers.

RECORD keeping and reporting

MONITORING of the surveillance system

rehabilitation. Programs should be implemented on educating patients and other community members about basic public health aspects of arsenicosis and to dispel misconceptions that may lead to stigmatization, family and occupational disruption and other social hardsdhip.

6.03 PATIENT MANAGEMENT FLOW CHART

A suggested patient management schedule is illustrated in *Flowchart 2*. The implementation of this flowchart will depend on both the guiding national policy and the existing infrastructure in a particular country. The first step, examination of the patient for the presence of non-cancer arsenic-related skin lesions, may be conducted by trained health care personnel such as medical doctors or other skilled health care providers at the primary care level. These personnel should receive standardized training in the recognition of characteristic arsenic-related skin lesions. In order to maximize sensitivity of the case detection process at the primary health care level, the personnel are instructed to exercise an inclusive and non-stringent approach when identifying arsenic-related skin lesions.

Patients who are designated "probable cases" should be referred for a second evaluation by a dermatologist or other physician with specialized expertise in the recognition and diagnosis of arsenic-related skin lesions and other abnormal conditions of the skin. This evaluation, which should include a complete physical examination and a review of the patient's medical and exposure history, may be conducted at either the primary or secondary care level. The purpose of the secondary examination is two-fold:

(a) The criteria outlined in *Table 2* and *Section 9* should be used to perform a differential diagnosis to either confirm or rule out the presence of skin lesions consistent with chronic arsenic exposure;

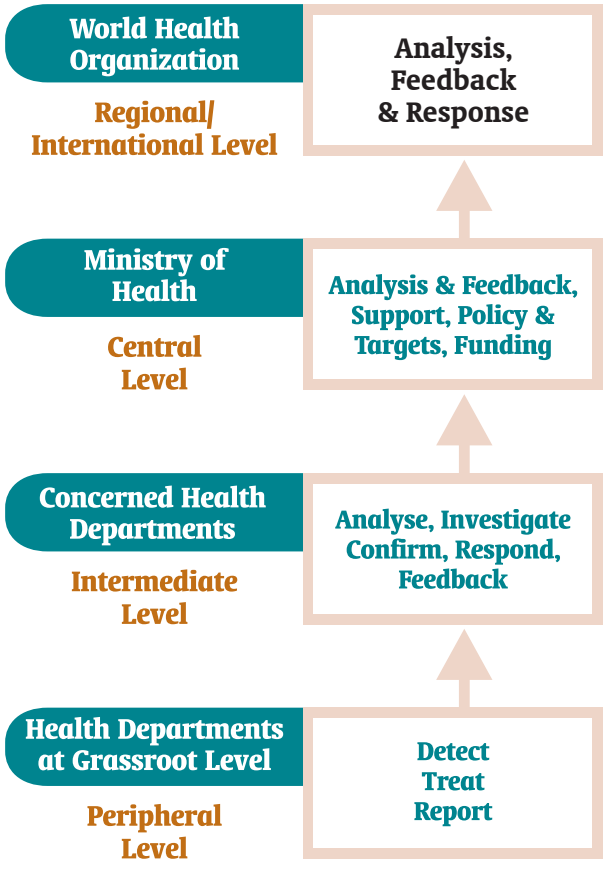
and

(b) The patient should be evaluated for the presence of other medical conditions potentially related to arsenic exposure (*Table 3*). All patients should be referred, as appropriate, for further evaluation or treatment of any medical conditions detected by the medical specialist.

If the patient's clinical presentation is such that the medical specialist cannot confirm or rule out the presence of characteristic skin lesions, the patient should retain the diagnosis of "suspected/probable case", and be referred for re-evaluation by the medical specialist in 6 to 12 months.

Section 7. Case Surveillance

Figure 2
COMPONENTS OF SURVEILLANCE TASKS AT EACH ADMINISTRATIVE LEVEL



7.01 RATIONALE OF SURVEILLANCE

Surveillance is the routine collection, analysis, interpretation and distribution of data relevant for control and prevention. Two types of surveillance can be recognized: active and passive. An active surveillance is solicited by the health agency and the cases are actively sought using a variety of methods such as case-search or calling up the health care provider. A passive surveillance is one which is initiated by the health care providers and cases are routinely sent to the health agency. There are three prerequisites to public health surveillance: (1) an organized health system, (2) a classification system of the disease or conditions under surveillance and, (3) measurement techniques.

Each Member Country has a health system. For sustainability, arsenicosis surveillance should be included in the routine reporting format that can be grafted into the disease surveillance system of each country.

The WHO classification provides a broad system for classifying arsenic cases, and can be accordingly adapted to the specific needs of a country.

The measurement techniques pertain to the process of surveillance consisting of collecting data for information and action. For this purpose, data is collected, collated, analysed and interpreted. The results are then disseminated to facilitate prevention and control measures.

The goals of arsenic surveillance must be defined by the respective national authorities as these will depend on the availability of resources and infrastructure for implementation. Since resource is a constraint, active search for arsenicosis cases should only be undertaken where the magnitude of the problem needs to be assessed. Furthermore, arsenicosis is a chronic condition and is not targeted for eradication. Therefore, passive surveillance or sentinel surveillance from arsenic clinics may be sufficient from a public health point of view. The main goal of arsenicosis surveillance then becomes follow-up and management of cases, especially “probable” cases that cannot be easily classified. Surveillance can

also be used to monitor the effectiveness of an intervention programme such as behaviour change or introduction of safe water options.

7.02 SUGGESTED FORMAT OF SURVEILLANCE

Clarity of purpose is essential for effective surveillance. The following criteria are recommended for surveillance:

(1) Clear objectives of the programme;

(2) Specification of the target population under surveillance;

(3) Realistic programme indicators of surveillance;

(4) Specification of the minimum data set to be used;

(5) Clear guidelines on the tasks and role of each health care provider in the chain of surveillance; and

(6) Enabling tools and guidelines to be used in performing surveillance tasks.

Each country must decide whether the objective of the arsenic surveillance programme is to monitor the trend of the arsenicosis or to follow up patients for clinical management. These two goals are not mutually exclusive but the associated tasks are different. Depending on the surveillance objectives one can select the appropriate target population to be either all subjects at risk for arsenic diseases or only subjects at high risk. The indicator for the surveillance programme will also be contingent on the objectives of the programme. Thus, if all subjects are under surveillance, then one can express the indicator as the number of new cases of arsenic per 100,000 population for a given period.

A minimum core data set should be collected. The data may consist of who is a case, specified by age and sex. What type of case is it, classified according to the WHO algorithm of suspected, probable, clinically confirmed, clinically and laboratory confirmed or unclassified. Where is the case located, based on the geographical location. How is the case, depending on whether it is alive, dead, or has other major complications.

The surveillance tasks must be defined for each administrative level of the health service. Figure 2 shows the surveillance tasks for each level of the health care delivery. Thus, at the peripheral levels of health care, the focus should be to detect "suspected" and "probable" cases as well as to report and provide symptomatic treatment of systemic infections. Therefore, surveillance information may be kept case by case at the primary level.

At the intermediate, administrative level of health care, the focus would be to clinically confirm all "suspected" and "probable" cases as well as to provide clinical management of Bowen's disease and systemic disorders. The surveillance data must be analysed to monitor trends and provide feedback to the primary levels for programme implementation. The data may be kept in an aggregate form at this level.

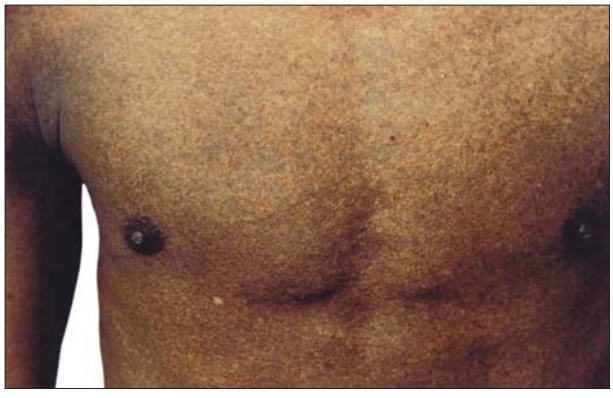
At the central level, the focus should be on confirming all categories of cases and monitoring the overall performance and trends of the surveillance system by the use of graphs, maps, charts and trends. The data should be kept in aggregate form at this level and reporting should include submission of periodic reports to WHO and other relevant agencies.

Each Member Country should formulate appropriate tools, guidelines and protocols for reporting cases. This will allow data flow from the primary to the tertiary level and specify how frequently the data will be reported and in what formats (electronic, paper, or telephone). The data will flow from one administrative level to another. Case detection to be used must be clearly specified. It is recommended that detection and reporting of cases be implemented using the WHO hierarchical case classification system as discussed in *Section 4* of this module and the flowchart shown on page 12-13 *(Gatefold)*.

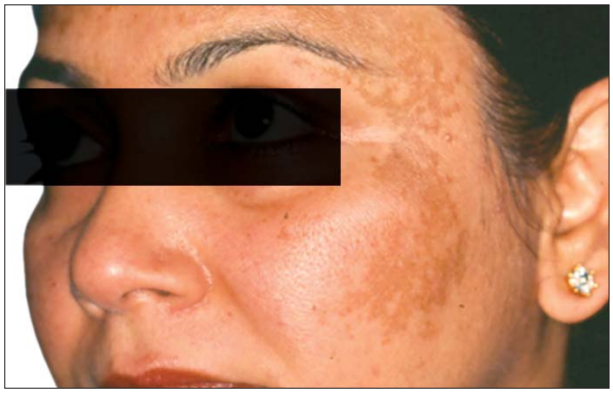
Section 8. Illustrations of Skin Manifestations

DIFFUSED MELANOSIS

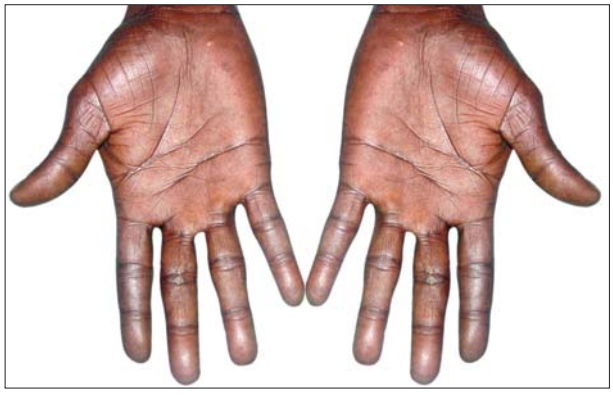
Nearly all arsenicosis patient first show diffused melanosis that gradually appears over the palms, soles, face and skin. This condition has to be distinguished from melanosis of genetic or environmental origin, for further details see Table 2 and section 9.



Diffused Arsenical Melanosis
Chest

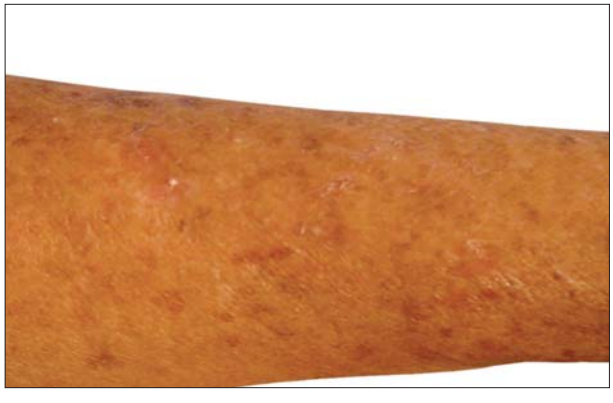


Non-Arsenical Diffused Melanosis
Melasma is usually confined to face to person with hormonal dysfunction

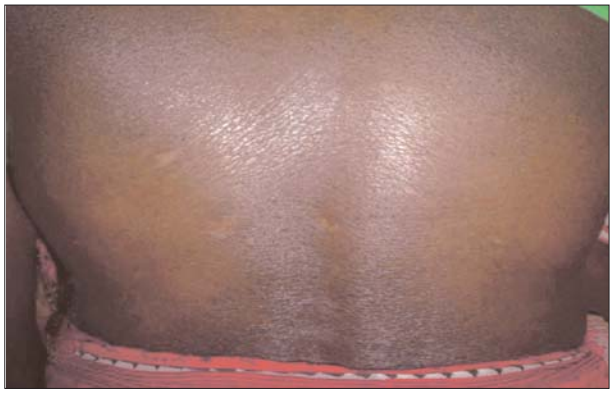


Diffused Arsenical Melanosis
Hands

Non-Arsenical Diffused Melanosis
Ashy Dermatosis is confined to the face and trunk



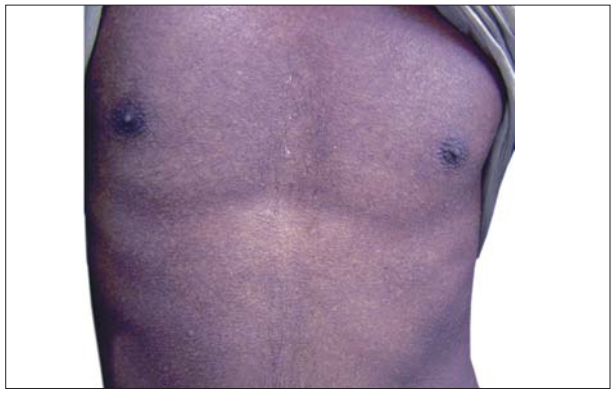
Non-Arsenical Diffused Melanosis
Actinic Dermatosis is confined to exposed part of the body



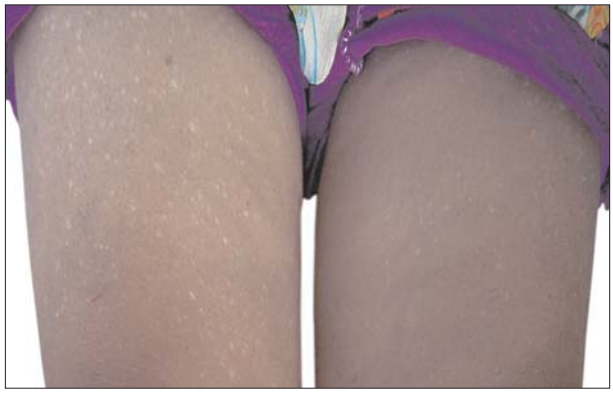
Non-Arsenical Diffused Melanosis
Icthyosis is confined to the back

LEUCO-MELANOSIS

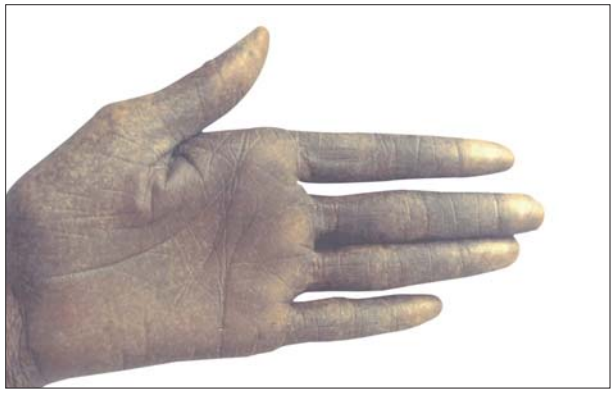
Some arsenicosis patients show Leukomelanosis appearing as "rain-drops", usually consisting of a mixture of pigmented dark cells and white, de-pigmented cells that occur in the chest, backs and legs. Arsenical Leukomelanosis has to be distinguished from leuko-melanosis of genetic or environmental origin, for further details see Table 2 and section 9.



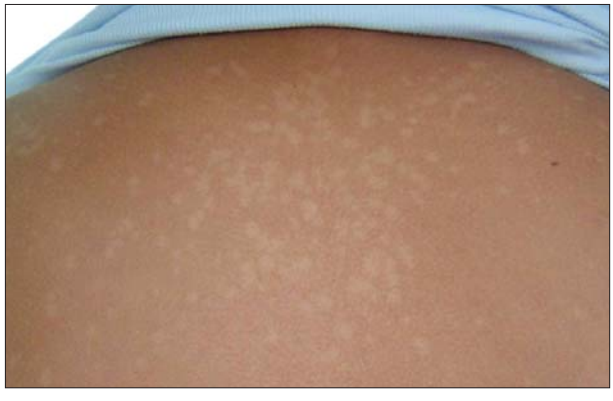
ARSENICAL-LEUKOMELANOSIS
Chest



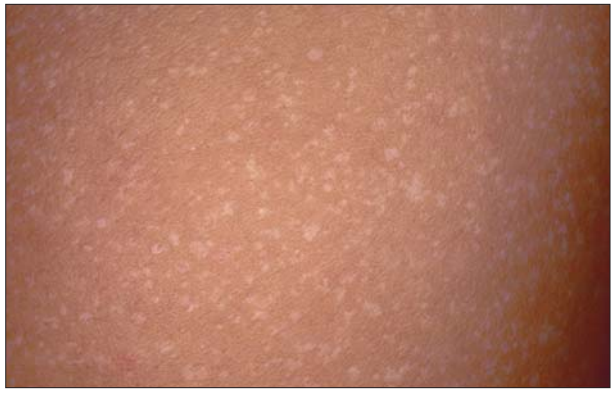
ARSENICAL-LEUKOMELANOSIS
Thigh



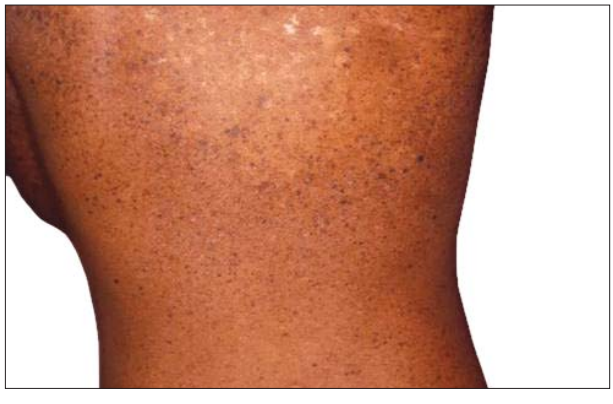
ARSENICAL-LEUKOMELANOSIS
Palm



NON-ARSENICAL-LEUKOMELANOSIS
Pityriasis versicolor of the back is characterized by hypopigmented macules with fine scales



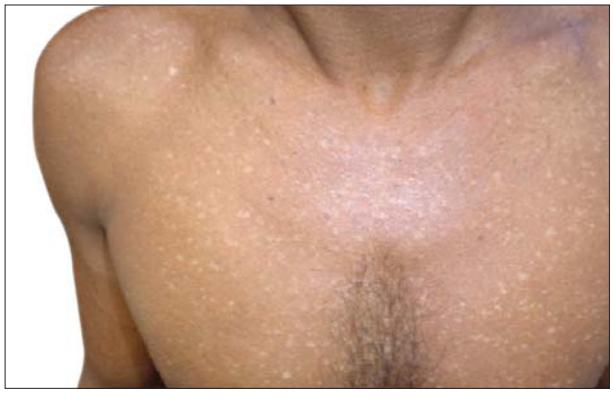
NON-ARSENICAL-LEUKOMELANOSIS
Idiopathic guttate hypomelanosis is characterized by discrete, slightly depressed macules of white porcelain color



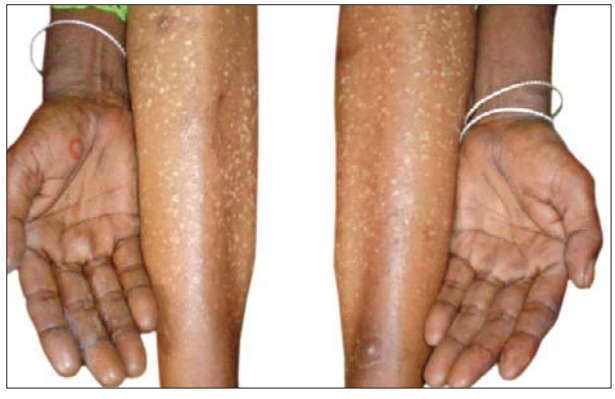
NON-ARSENICAL-LEUKOMELANOSIS
Xeroderma pigmentosa is characterized by freckling and atropic depigmentation

SPOTTED MELANOSIS

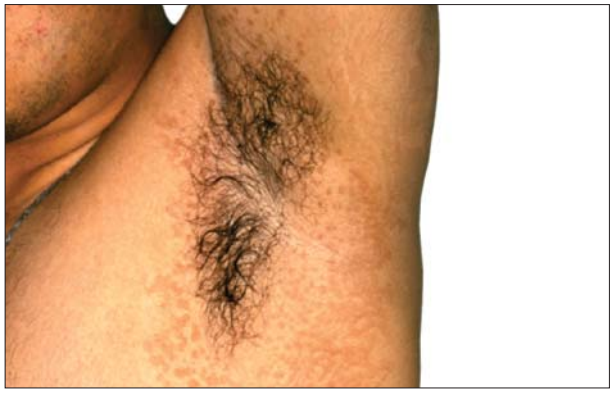
Many arsenicosis patients show spotted melanosis that appears mainly on the chest, backs and thigh. This condition has to be distinguished from other types of spotted melanosis of genetic or environmental origin, for further details see Table 2 and section 9.



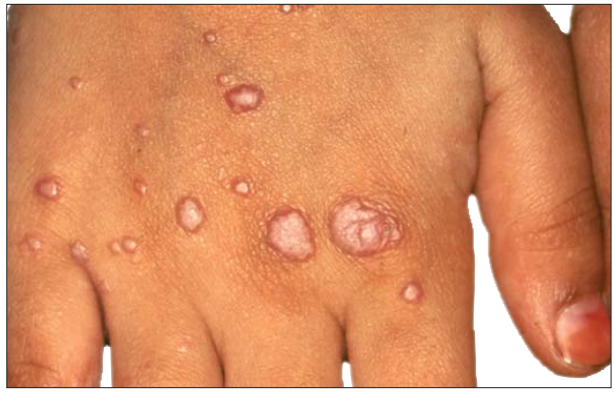
SPOTTED ARSENICAL MELANOSIS
Rain-drop pigmentation chest



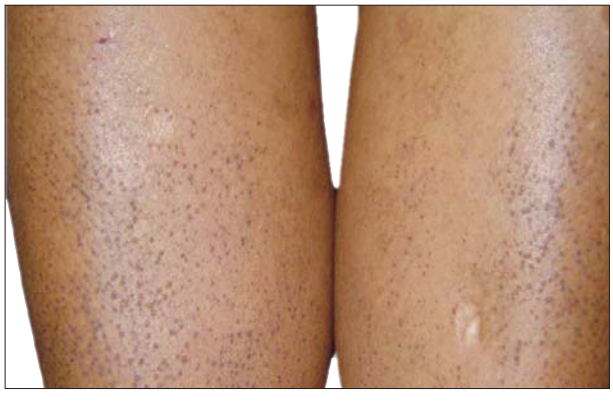
SPOTTED ARSENICAL MELANOSIS
Rain-drop pigmentation legs



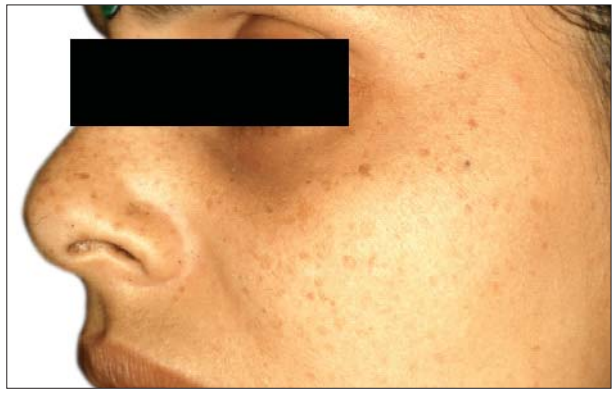
NON-ARSENICAL SPOTTED MELANOSIS
Pityriasis versicolor is charcterized by hyper-pigmented papules



NON-ARSENICAL SPOTTED MELANOSIS
Lichen planus is characterized by violaceous pigmentation



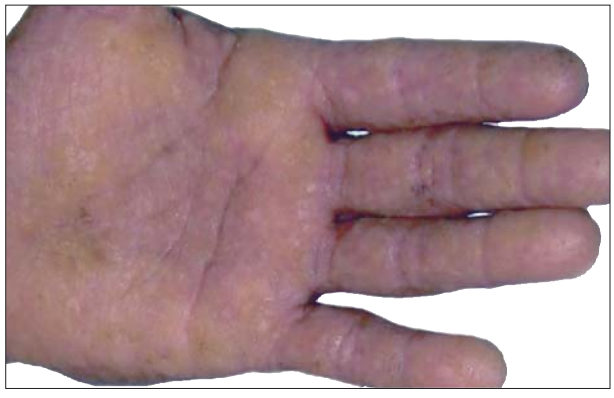
NON-ARSENICAL SPOTTED MELANOSIS
Lichen amyloidosis is characterized by angular melanosis of the trunks



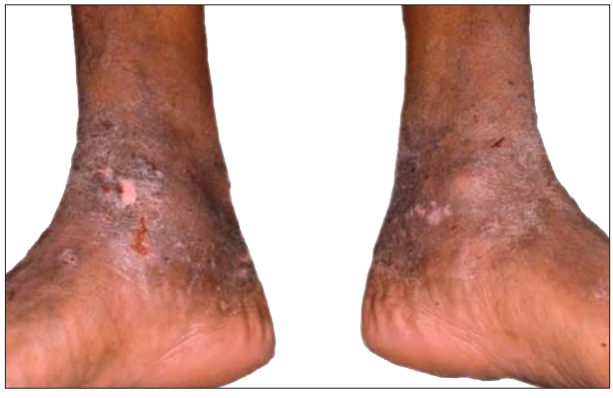
NON-ARSENICAL SPOTTED MELANOSIS
Freckles is characterized by mottled pigmentation

DIFFUSED KERATOSIS

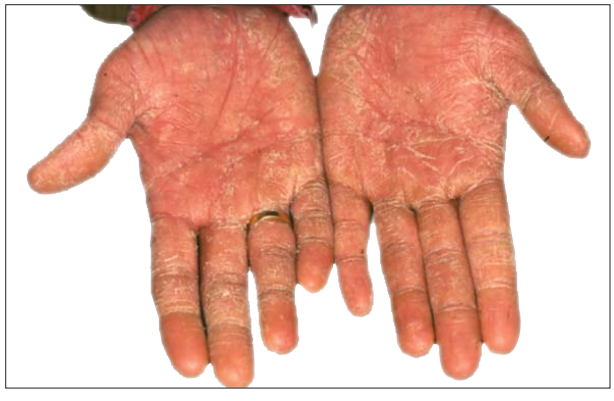
Arsenical diffused keratosis are hyperkeratotic lesions that have diffused in all parts of the sole and palms giving a gritty feeling to the touch and have to be distinguished from other non-arsenical keratosis of genetic or environmental origin, for further details see Table 2 and section 9.



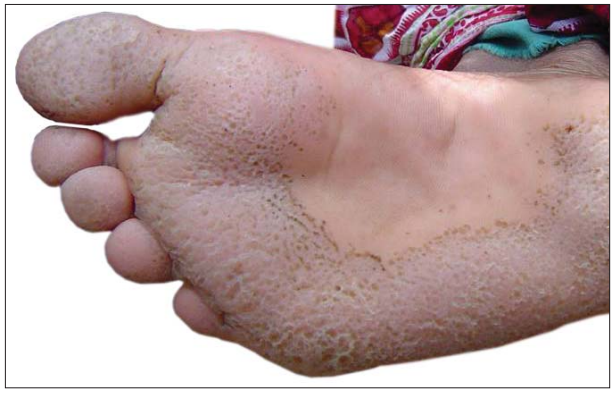
DIFFUSED ARSENICAL KERATOSIS
Hands



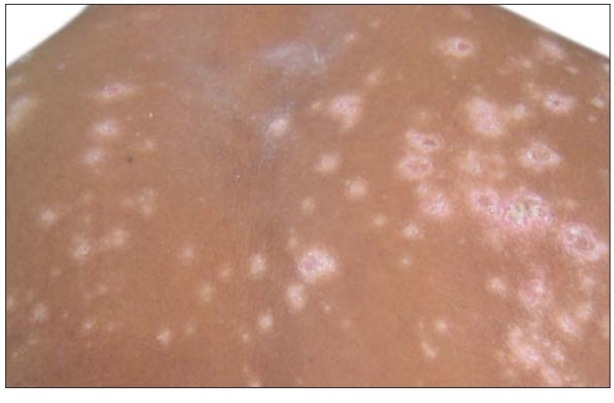
NON-ARSENICAL DIFFUSED KERATOSIS
Eczema is characterized by oozing lichenified lesions



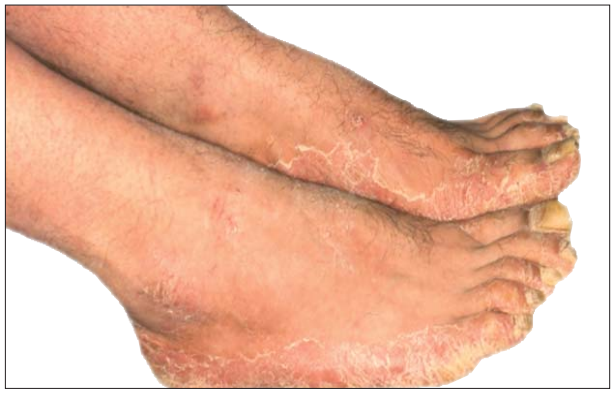
NON-ARSENICAL DIFFUSED KERATOSIS
Psoriasis is characterized by kerato-derma giving scaly patches (hand)



NON-ARSENICAL DIFFUSED KERATOSIS
Pitted Keratolysis is characterized by pitted or depressed lesions



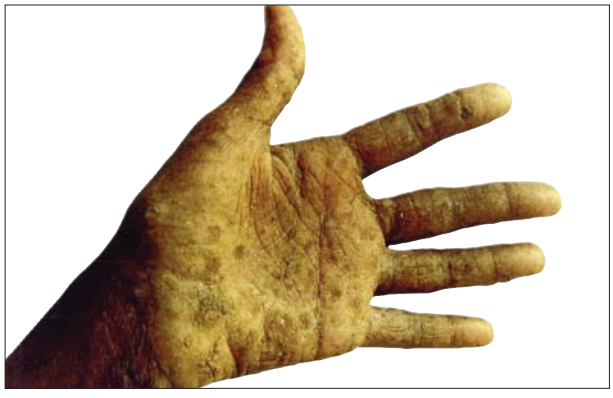
NON-ARSENICAL DIFFUSED KERATOSIS
Psoriasis is charcterized by kerato-derma giving scaly patches (back)



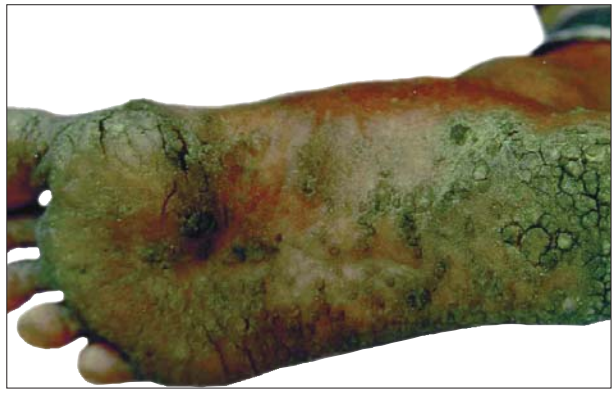
NON-ARSENICAL DIFFUSED KERATOSIS
Tinea Pedis is characterized by scaly, fissured, keratotic lesions

NODULAR KERATOSIS

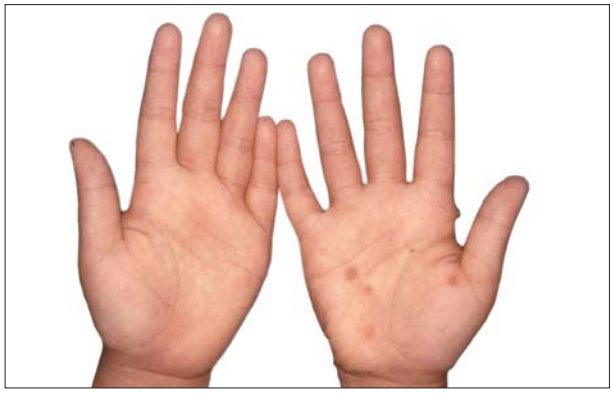
Many arsenicosis patients show hyperkeratotic, pin-headed lesions that occur as localized lesions in parts of the palms and soles. This condition has to be distinguished from other non-arsenical nodular keratosis of genetic or environmental origin, for further details see Table 2 and section 9.



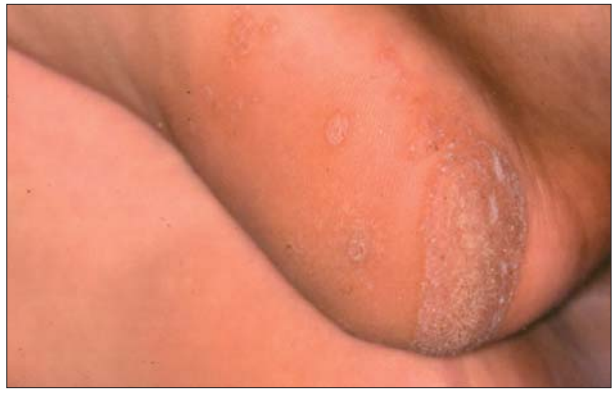
ARSENICAL NODULAR KERATOSIS
Hand



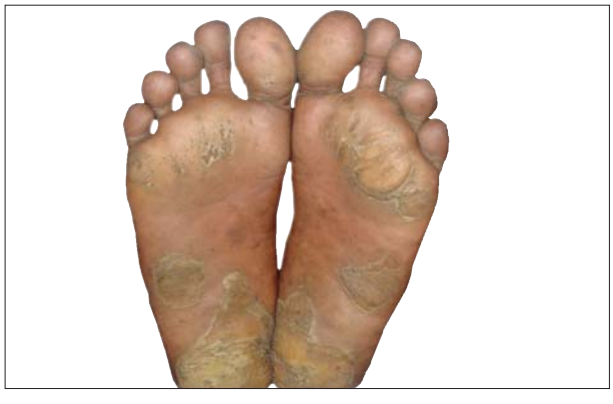
ARSENICAL NODULAR KERATOSIS (WITH MELANOSIS)
Feet



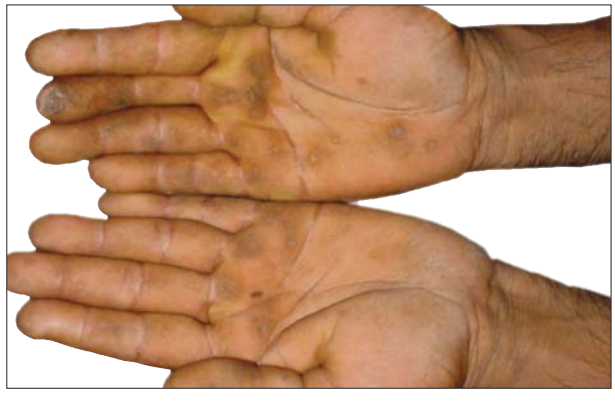
NON-ARSENICAL NODULAR KERATOSIS
Verruca vulgaris appears as verrucous papules (hands)



NON-ARSENICAL NODULAR KERATOSIS
Verruca vulgaris appears as verrucous papules (feet)



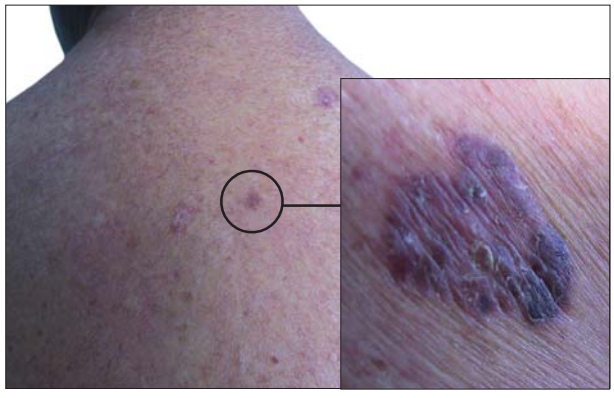
NON-ARSENICAL NODULAR KERATOSIS
Callus are corns occuring at sites of friction



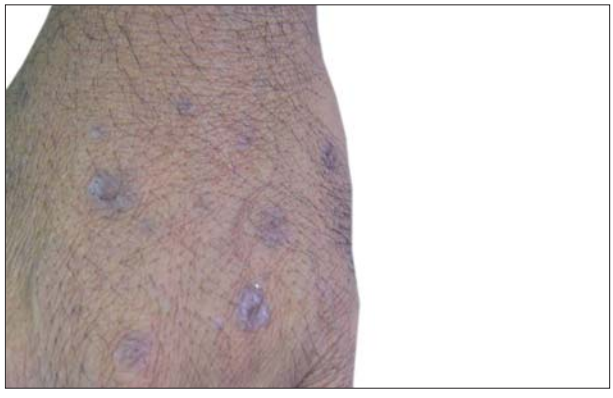
NON-ARSENICAL NODULAR KERATOSIS
Occupational keratosis, showing lesions at sites of friction

PRE-MALIGNANT AND MALIGNANT CUTANEOUS CONDITIONS

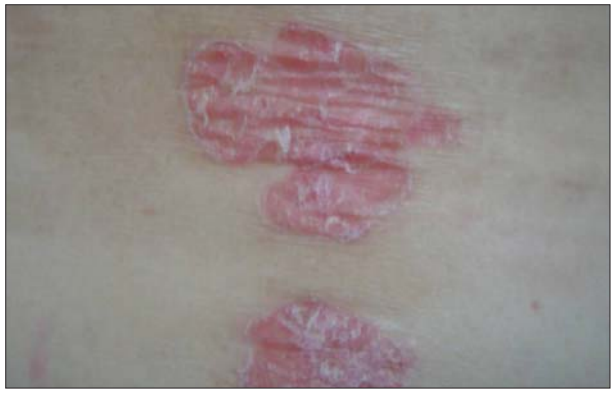
Pre-malignant and malignant cutaneous conditions associated with arsenic exposure have to be distinguished from other similar conditions.



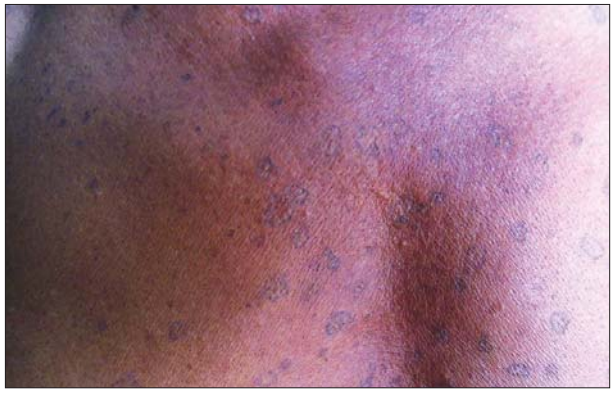
BOWENS DISEASE
Bowens disease occur as multiple-crusted, erythematous papules and plaques (back)



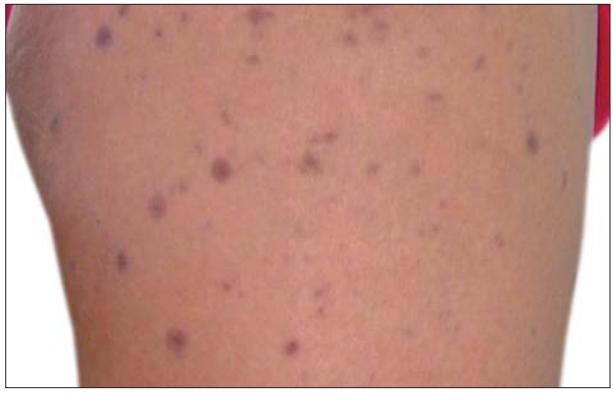
NON-BOWEN DISEASE
Lichen planus of hands showing flat-topped violaceous papules



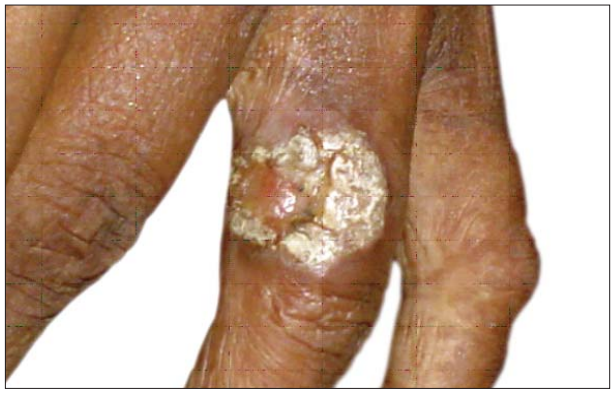
NON-BOWEN DISEASE
In psoriasis, the lesions are sharply demarcated with silvery scales



NON-BOWEN DISEASE
In Superficial Actinic Prokeratosis, the lesions are ill defined and reddish brown in color



NON-BOWENS DISEASE
Lichen planus of legs showing violaceous papules (thighs)



SQUAMOUS CELL CARCINOMA
Squamous cell carcinoma is characterized by crusted plaques with ill-defined borders

Section 9. Further Discussions on Differential Diagnosis

DISEASE ASSOCIATED WITH PIGMENTARY CHANGES	MAIN CUTANEOUS MANIFESTATIONS	KEY FEATURES THAT DISTINGUISH THE CONDITION FROM ARSENICOSIS
Melasma	Brown patches typically on the malar prominences of face and forehead. The pigmented patches are sharply demarcated. Mainly in women, particularly in pregnancy, on birth control pills or with ovarian dysfunction.	Patchy pigmentation in arsenicosis is uncommon on the face, and does not vary with pregnancy.
Drug-induced	Post inflammatory hyper-pigmentation in individuals with past history of taking an offending drug. The sites and morphology of the lesions vary according to the responsible drug. Commonly, pigmentation occurs on sun-exposed areas of skin, and also on mucous membranes, particularly the gingiva and hard palate. The pigmentation varies from blue black, muddy brown, pink, brown, or slate-grey colour depending on the drugs used. There may be changes on the nails. Pigmentation usually fades away after withdrawal of the drug.	Hyper-pigmentation in arsenicosis is not localized or concentrated in sun-exposed areas, and rarely involves the mucous membranes. Presence of keratosis in Arsenicosis.
UV induced Pigmentation/ Actinic dermatosis	Darkening of sun-exposed areas of the skin following exposure to sunlight. The increased pigmentation occurs over hours to days, and fades gradually over the course of days to weeks when UV exposure is discontinued.	Hyper-pigmentation in arsenicosis is not localized or concentrated in sun-exposed areas, and does not increase or decrease with changes in the intensity of UV exposure.
Xeroderma pigmentosum	Genetic disorder, found mostly in children. Characterized by intensive freckling, with atrophic depigmented skin changes, photophobia and kerato-conjunctivitis, leading to blindness. A positive family history is of diagnostic value.	Arsenicosis is not associated with ocular signs or symptoms, except in early transient conjunctival injection.
Familial progressive dyschromatosis	i) Lesions run in families ii) Lesions are either spotted, freckle-like melanosis or symmetrical diffuse melanosis iii) Predominantly involve extremities iv) May also involve trunk.	Arsenicosis does not run in generations and is associated with keratosis.
Pityriasis versicolor	Hyper and hypo-pigmented macules with fine scales and raised margins, usually on trunk, proximal extremities, face, and neck. The scales are dusk-like or furfuracious. May be exacerbated by sunlight. Wood's lamp examination is helpful for diagnosis, showing yellowish fluorescence. Skin scrapings obtained for microscopy and mycological culture reveal fungal elements.	Pigmented macules in arsenicosis are not raised, and do not vary with sunlight. Fungal elements are absent.
Idiopathic guttate hypomelanosis	Porcelain-white macules with distinct margins may be slightly depressed without any obvious cause.	Pigmented macules are not depressed in arsenicosis. No keratosis or melanosis is present in Idiopathic guttate hypomelanosis.
Pityriasis lichenoides chronica	i) Disease of adolescents and young adults ii) Starts as non-pruritic erythematous papules, becomes covered with pigmented scales	Scales are distinctive and absent in arsenicosis; there is no keratosis in Pityriasis lichenoides chronica.

DISEASE ASSOCIATED WITH PIGMENTARY CHANGES	MAIN CUTANEOUS MANIFESTATIONS	KEY FEATURES THAT DISTINGUISH THE CONDITION FROM ARSENICOSIS
Pityriasis lichenoides chronica (contd.)	iii) Scales are lid-like iv) Lesions resolute with hypo-pigmented macular lesions (like pityriasis versicolor) v) Trunk and extremities are common sites of involvement vi) Recalcitrant in nature.	
Leprosy	Macular hypo-pigmented or erythematous lesions, usually with loss of sensation. There may be involvement of peripheral nerves which are usually thickened and enlarged. In advanced stage there may be muscle atrophy and deformities. Slit skin smear and skin biopsy will confirm the diagnosis.	Dermatological lesions of arsenicosis are rare on the face, and are not associated with atrophy or deformity and loss of sensation.

DISEASE ASSOCIATED WITH KERATOTIC CHANGES	MAIN CUTANEOUS MANIFESTATIONS	KEY FEATURES THAT DISTINGUISH THE CONDITION FROM ARSENICOSIS
Seborrheic keratosis	i) Pigmented keratotic lesions found mostly on photo exposed areas. Covered site may also be involved ii) Asymptomatic in nature iii) Stuck on skin surface iv) Old age group commonly involved.	In arsenicosis there is presence of speckled, diffuse or leuco-melanosis and keratosis of palm and sole.
Hereditary Palmo-plantar hyperkeratosis	Dominantly inherited disorder presenting with marked congenital thickening of the palms and soles, usually symmetrical and diffuse. There is frequently hyper-hydrosis and occasional nail thickening.	Arsenical keratosis is not a congenital condition, but appears gradually over a period of years to decades.
Epidermodysplasia veruciformis	a) Hypo-pigmented macular lesions interspersed between keratotic lesions, asymptomatic. b) Keratotic papular lesion mainly in trunk sparing palm, sole, asymptomatic. Transform into: a) Cutaneous horn b) Bowen's disease c) Squamous cell Ca	Arsenical keratoses do not spare keratosis of palm and sole.
Eczema	Usually, but not always associated with history of contact with household or occupational allergen. Manifested by papulo-vesicular, oozy, crusted lesions in acute stage, progressing to lichenified, thickened, scaly lesions in chronic stages. Pruritus is common. Withdrawal of allergen may be associated with remission.	Arsenical keratosis occurs predominantly on palms and soles, and lacks an acute, papulo-vesicular stage. Pruritus is not a common feature.

DISEASE ASSOCIATED WITH KERATOTIC CHANGES	MAIN CUTANEOUS MANIFESTATIONS	KEY FEATURES THAT DISTINGUISH THE CONDITION FROM ARSENICOSIS
Verruca (warts)	Usually occurs on the dorsal surface of hands and feet, particularly on the periungual region. Caused by a human papillomavirus, trimming the papular rough surface keratin makes the capillaries more prominent and visible, which may help in diagnosis. Spontaneous resolution may occur.	Arsenical keratosis occurs as multiple or diffuse lesions, predominantly on palms and soles. Lesions are pinpoint in early stages, but may form wart-like nodules in advanced cases.
Lichen Planus	i) Generally localized lesion, sometimes may be linear or involve scalp ii) Lesions are papules, mostly on extremities and follicular in nature iii) Heals with pigmentation, atrophy or loss of hair.	Absence of keratotic follicular lesions in arsenicosis.
Corns and calluses	Keratotic thickening that occurs on pressure points in hands and feet. May be painful to palpation.	Arsenical keratosis of palms and soles is not confined to pressure points.
Occupational keratosis	Related with nature of occupation. Occurs on palm and sole on areas that come in contact with occupational tools, usually sparing the mid portion.	Arsenic keratoses are distributed evenly.
Tinea pedis and other mycoses	Maceration, scaling, thickening and fissuring, usually in front part of the soles and intertriginous regions. Pruritus is a prominent feature. Fungal elements may be detectable on microscopy or mycological culture.	Arsenical keratosis is not prominent in intertriginous areas, and is usually without prominent pruritus.
Psoriasis	Discrete, erythematous, dry scaly papulo pustular lesions or plaque type lesions, usually on the middle portion of palm and sole with or without itching. Typical silvery white scaly patches may be present elsewhere on the skin. Nails are also affected with pitting, subungual hyperkeratosis or onycholysis. Characterized by relapse and remission.	Arsenical keratosis is without erythematous or papulo pustular features.
Pityriasis rubra pilaris	Characterized by symmetrical and diffuse spiky papular eruptions on extensor surface of skin particularly on elbows, knees and hands (Nutmeg grater). Frequently leads to exfoliative dermatitis. Hyperkeratosis in palms and sole is remarkable. On sole hyperkeratosis extends up the sides called “Sandal”. There may also be nail changes.	Arsenical keratosis occurs predominantly on the palms and soles, and lacks exfoliate features.
Candidial hyperkeratosis/pitted keratolysis	i) Diffuse keratosis ii) Sieve-shaped depressed lesion, exclusively on the soles iii) Found in barefooted persons with excessive water users.	In arsenicosis the keratotic soles are not pitted, and there will be associated with skin pigmentation.
	i) Solitary or multiple discrete papulonodular lesion with rough or verrucous surface ii) Generally unilateral iii) Multiple black dots at the centre iv) Bleeds on cutting / paring	

Appendix A: Working Methods Adopted for Formulation of the Field Guide

The accompanying flowchart illustrates the process and fundamental approaches that were used in developing this Field guide on the basis of the best available evidence.

Starting in 2000, the literature was extensively reviewed for all explicit and implicit case definitions and patient management strategies used so far and the most commonly occurring features were selected. These were used as the basis to formulate a working case definition and management protocol. At least 33 different published studies from around the world were used.

In 2002, Member Countries were supported to develop national case definition and management protocols. For this purpose, meetings of national expert committees consisting of dermatologists, oncologists, internists, toxicologists and epidemiologists were convened to arrive at a consensus.

In 2003, these national expert committees met in the Regional Office to reach a regional consensus based on the respective national protocols. The consensus version was field-tested in high and low prevalence areas. A committee of regional experts examined the results of the validation and prepared the present version of the protocol.

In 2004, this module was officially launched in Comilla, Bangladesh.

Figure 3
SUMMARY OF WORKING METHODS

Appendix B: Members of Expert Committees

List of members of Expert Committees that contributed to the formulation of this Field Guide

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