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"SKIN TOXICOLOGY"

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ABSTRACT:

The skin is the bodys largest and protective oragan covering entire body. The skin is the largest organ in the body and has a surface area of about 1.5-2 m² in adults. In certain areas, it contains accessory structures: glands, hair and nails. Many disorders act on skin viral infections, bacterial infection, fungal infection, non inflammetery conditions our skin is daily expose to substances many of which are neutral and safe while other are potentially harmful. In order to estimate of the degree of toxicity and damage to the skin tissues when exposed to harmful substances, skin toxicology study is required. Toxicology testing also known as safety assessment. In this project we can study skin tissue modes absorptions, corrosion, irritation and sensitization.

Key words: Skin, Protective, Toxicology, Safety assessment.

INTRODUCTION

Skin

The skin is the body's largest organ. It covers the entire body. It serves as protective shield against heat, light, injury, and infection. The skin also:

- Regulates body temperature
- Stores water and fat
- Is a sensory organ
- Prevents water loss
- Prevents entry of bacteria
- Acts as a barrier between the organism and its environment
- Helps to make vitamin D when exposed to the sun

- Structure of the skin

The skin is the largest organ in the body and has a surface area of about 1.5-2 m^2 in adults. In certain areas, it contains accessory structures: glands, hair and nails.

- Layer of skin :

- The epidermis, the outermost layer of skin, provides a waterproof barrier and createour skin tone.
- The dermis, beneath the epidermis, contains tough connective tissue, hair follicles, and sweat gland
- The subcutaneous tissue (hypodermis) is made of fat and connective tissue.

Epidermis	The epidermis is the thin outer layer of the skin. It consists of 3 types of cells: • **Squamous cells.** The outermost layer is continuously shed is called the stratum corneum. • **Basal cells.** Basal cells are found just under the squamous cells, at the base of the epidermis. • **Melanocytes**. Melanocytes are also found at the base of the epidermis and make melanin. This gives the skin its colour
Dermis	The dermis is the middle layer of the skin. The dermis contains the following: • Blood vessels • Lymph vessels • Hair follicles • Sweat glands • Collagen bundles • Fibroblasts • Nerves • Sebaceous glands The dermis is held together by a protein called collagen. This layer gives skin flexibility and strength. The dermis also contains pain and touch receptors.

Subcutaneous fat layer	The subcutaneous fat layer is the deepest layer of skin. It consists of a network of collagen and fat cells. It helps conserve the body's heat and protects the body from injury by acting as a shock absorber.

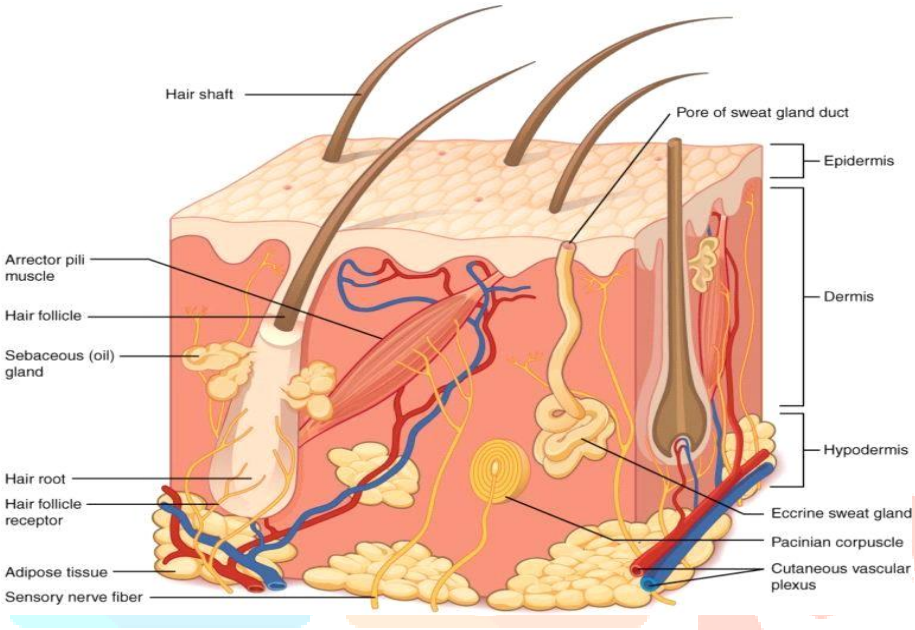

Fig. No. 1 structure of skin

- **Type of skin**

1.Normal skin 2.Oily skin
3.Dry skin
4.Combination skin 5.Sensitive skin

- Normal skin

Normal skin is also called eudermic. This means it is well-balanced. Normal skin is neither too oily nor too dry. It has balanced sebum production and good blood circulation.

Identify by:

- Smooth texture
- Fine pores
- No sensitivity
- No blemishes
- Few or no breakouts
- Radiant complexion

- Oily skin

Oily skin is characterized by a greasy appearance. This skin type is prone to acne breakouts. Oily skin is the result of excess sebum production. This type of skin has excess oil secretion and is mostly shiny, sweaty, and more prone to suffer from acne, blackheads, etc.

- Open/Big pores
- Prone to breakouts
- Blackheads, other blemishes, etc.

- Dry skin

Dry skin is determined by flaky and rough texture. It can at times feel tight and cause irritation. lack of moisture in the skin can result in a flaky and rough appearance. This is called dry skin. Dry skin tends to produce less oil and lacks vitality. This type of skin is exposed to dryness and is vulnerable to weather changes.

- Flaky and rough skin
- Uneven texture
- Itching
- Skin feels tight
- More visible lines
- Less elasticity in skin

- Combination skin

Combination skin is a mix of oily skin and dry skin. Usually in combination skin types, the T-zone is oily and the cheeks are dry. This type of skin needs to be well protected from sunlight as it is oilier than other types of skin and sensitive to sun damage.

Identify by:

Oily T-zone

And dry cheeks Breakouts only on forehead, chin and noseSensitive cheeks

Shiny skin

- Sensitive skin

If your skin flushes with spicy food and adversely reacts to new products you may have sensitive skin Skin that's easily irritated and is more reactive than nor- mal skin is referred to as sensitive skin This type of skin is fragile, usually prone to heat, redness, itching, etc. and loses its barrier, thus allowing microorganisms and irritants to easily enter and leading to infections and allergic reactions.

Identify by:

- Skin feels itchy and tight
- Parts of your body have uneven texture
- Becomes oily in summers
- Gets dry in winters
- Reacts to skincare
- Becomes red after a hot water bath
- Feels itchy while wearing tight clothes

FUNCTION OF SKIN:

- Protection:

The skin forms a relatively waterproof layer, provided mainly by its keratinised epi- thelium, which protect deeper, more delicate structures. As an important non- specific defence mechanism it acts as a barrier against:

- invasion by micro-organisms chemicals
- physical agents, eg, mild trauma, ultraviolet light
- dehydration.

The epidermis contains specialised immune cells called dendritic (Langerhans) cells, which are a type of macrophage. They phagocytose intruding antigens and travel to lymphoid tissue, where they present antigen to T-lymphocytes, thus stimulating an immune response.

Abundant sensory nerve endings in the dermis enable perception, discrimination and location of internal and external stimuli. This allows responses to changes in the envi- ronment, eg, by reflex action (withdrawal) to unpleasant or painful stimuli, protecting it from further injury . The pigment melanin protects against harmful ultra- violet raysin sunlight.

- Regulation of body temperature:

Body temperature remains fairly constant around 36.8°C across a wide range of envi- ronmental temperatures ensuring that the optimal range for enzyme activity required for metabolism is maintained. In health, varia- tions are usually limited to between 0.5 and 0.75°C, although it rises slightly in the evening, during exercise and in women just after ovulation. To maintain this con- stant temperature, a negative feedback sys- tem regulates the balance between heat produced in the body and heat Jost to the envi-ronment.

- Heat production:

When metabolic rate increases, body temperature rises, and when it decreases body temperature falls. Some of the energy released during metabolic activity is in the form of heat; the most active organs produce most heat.

- Heat loss

Most heat loss from the body occurs through the skin. Small amounts are lost in ex- pired air, urine and faeces. Only heat loss through the skin can be regulated; heat lost by the other routes cannot be controlled. Heat loss through the skin is affected by the difference between body and environmental temperatures, the amount of the body sur- face exposed and the type of clothes worn. Air insulates against heat loss when trapped in layers of clothing and between the skin and clothing. For this reason sev- eral layers of lightweight clothes provide more effective insulation against low envi- ron- mental temperatures than one heavy garment.

- Control of body temperature:

The temperature regulating centre in the hypothalamus is sensitive to the temperature of circulating blood. This center respond to decreasing temperature by sending nerveimpulses to:

- arterioles in the dermis, which constrict decreasing blood flow to the skin
- skeletal muscles stimulating shivering.

As heat is conserved, body temperature rises and when it returns to the normal range again the negative feedback mechanism is switched off . Conversely when body tem- perature rises, heat loss is increased by dilation of arterioles in the dermis, increasing blood flow to the skin, and stimulation of the sweat glands causing sweating, until it falls into the normal range again when the negative feedback mechanism is and is switched off.

• Activity of the sweat glands. When body temperature increased by 0.25 to 0.5°C the sweat glands secrete sweat onto the skin surface. Evaporation of sweat cools the body, but is slower in humid conditions.

Loss of heat from the body by evaporation of water through the skin and expired air still occurs even when the environmental temperature is low. This is called insensible water loss (around 500 mL per day) and is accompanied by insensible heat loss.

• Regulation of blood flow through the skin: amount of heat lost from the skin de- pends largely on blood flow through dermal capillaries. As body temperature rises, the arterioles dilate and more blood enters the capillary network in the skin. The skin is warm and pink in colour. In addition to increasing the amount of sweat produced, the temperature of the skin rises and more heat is lost by radiation, conduction and convection.

If the environmental temperature is low or if heat production is decreased, the arteri- oles in the dermis are constricted. This reduces blood flow to the body surface, con- serving heat. The skin appears paler and feels cool.

Skin Disorders

- Infections
- Viral infections
  - Human papilloma virus

Haman papilloma virus (HPV) causes warts or verruca's which are spread by direct contact, e.g. from another lesion another infected individual. The epidermis proliferates and a small, firm growth develops, which is nearly always berg. Common sites are thehands, the face and the soles of the feet

  - Herpes viruses

Rashes seen in chickenpox and shingles are caused by the herpes zoster virus. Other herpes viruses cause cold sores (herpes simplex virus) and genital herpes (herpes sim-plex virus)

- Bacterial infections1)Impetigo

is a highly infectious condition commonly caused by Staphylococcus aureus. Superfi- cial pustules develop, usually und the nose and mouth. It is spread by direct contact and affects mainly children and immunosuppressed individuals. When caused by Strepto- coccus pyogenes (a group A Bhaemolytic streptococcus) the infection may be compli- cated by an immune reaction, causing glomerulonephritis a few weeks later.

2) Cellulitis

This is a spreading infection caused by some anaerobic teris, including Streptococcus pyogenes and Clostridium perfringens, which enter through a break in the skin. Their spread is facilitated by the formation of enzymes, which break down the connective tissue that normally isolates area of inflammation. If the infection is untreated, the bac- teria may enter the blood, causing septicaemia (sepsis).

In severe cases, necrotising fasciitis may occur. There is rapid and progressive necrosis of subcutaneous tissue that usually includes the fascia in the affected area. Multiple organ failure is common and mortality is high.

- Fungal infections (mycoses)

Fungal infections are more likely in warm mit skin, such as skin folds and between the so and immunocompromised individuals

- Ringworm and tinea pedis

These are superficial skin infections. In ring the a outward spreading ring of inflamma- tion with a dar path of apparently normal skin in the center. It most commonly affects the scalp, feet and groin and is easily spread to the Tinea pedis (athlete's foot) affects the skan between for toes Both infections are spread by direct contact

Diagram of fungal infection

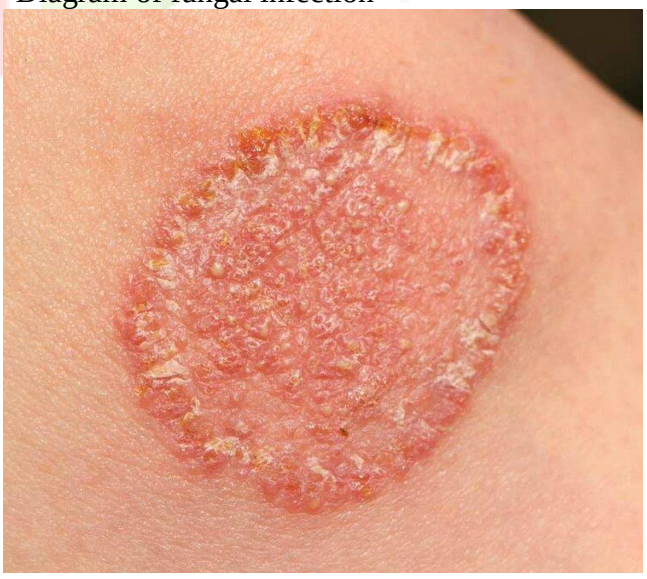

Fig.No. 2

- Non-infective inflammatory conditions

  - Dermatitis (eczema)

Dermatitis is a common inflammatory skin condition t may be either acute or chronic. In acute dermatit is redness, swelling and exudation of serous fruid, ally accompanied by pruritus (itching). This is often followed by crusting and scaling. If the condition

becomes chronic, the skin thickens and may become leathery due to long-term scratch- ing, which may cause infection.

- Atopic dermatitis

This is associated with allergy and commonly affects pic individuals, ie, those prone to hypersensitivity disorders Children, who may also suffer from hay fever or asthma areoften affected

- Contact dermatitis

This may be caused by direct contact with cosmetics, soap, detergent, strong acids or alkalis indul chemicals or a hypersensitivity reaction to latex, dyes and other chemicals,for example

  - Psoriasis

Genetic and environmental factors are implicated in the development of this common condition, which in characterised by exacerbations and periods of remissio of varying duration.

Trigger factors that worsen the condition include trauma, infection, sunbum and some drugs it is thought that anxiety and stress may also contribute in some individuals Pso- riasis is sometimes associated with rheumatoid arthrcharacteriz

Cell division in the basal layer of the epidermis increases so that new cells are pushed more quickly towards the surface layers.

Transit time (from basal to superficial layer may be as little as 5 days (instead of the normal 28 days that cells arriving at the surface have not had time to mature into kerat- inised squames common sites but other parts can also be affected.

  - Acne vulgari

This most frequently affects adolescent males and is thought to be caused by increased levels of testosterone after puberty. Sebaceous glands (in hair follicles) become blocked and then infected,

leading to inflammation and pustule formation In severe cases per- manent scarring may result.The most common sites are the face, chest and upper back

- Pressure ulcers

Also known as decubitus ulcers or bedsores, these occur over 'pressure points, areas where the skin may be compressed for long periods between a bony prominence and a hard surface, eg, a bed or chair.

When this occurs, blood flow to the affected area is impaired and ischaemia develops. Initially, the skin reddens and later, as ischaemia and necrosis occur, the skin sloughs and an ulcer forms, which may then enlarge into a cavity.

If infection occurs, this can result in sepsis. Healing takes place by secondary intention Predisposing factors may be. extrinsic, eg pressure, shearing forces, trauma, immobil- ity, moisture, infection intrinsic, e.g. poor nutritional status, emaciation, incontinence, infection, concurrent illness, sensory impairment, poor circulation.

- Burns

Burns may be caused by many types of trauma, including heat, cold, electricity, ionising radiation and corrosive chemicals, such as strong acids or alkalis (bases). Local damage occurs, disrupting the structure and functions of the skin.

- Burns are classified according to their depth:

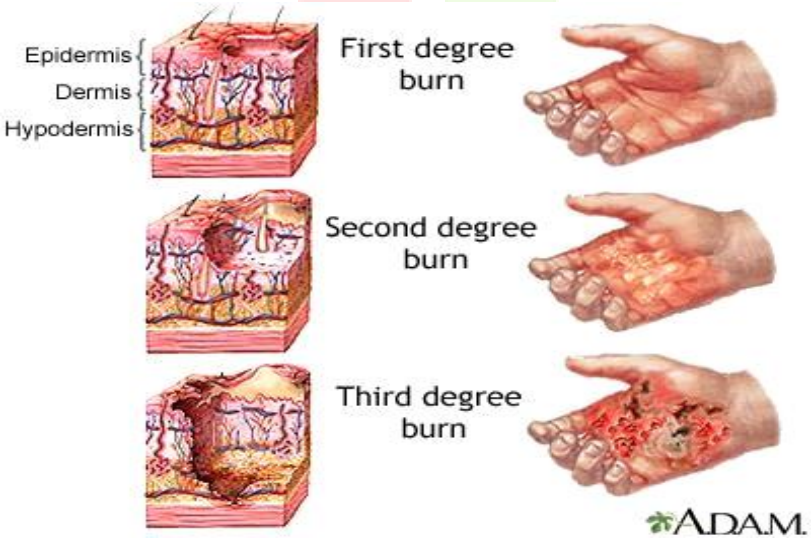

Fig.No.3

• first degree when only the epidermis is involved, the surface is moist and there are signs of inflammation including redness, swelling and pain. There are no blisters and tissue damage is minimal.

• second degree when the epidermis and upper dermis are affected. In addition to the signs and symptoms above, blistering is usually present.

• Third third degree (deep or full thickness) when the epidermis and dermis are de- stroyed. These burns are usually relatively painless as the sensory nerve endings in the dermis are destroyed. After a few days the destroyed tissue coagulates and forms an eschar, or thick scab, which sloughs off after 2 to 3 weeks.

In circumferential burns, which encircle any area of the body, complications may arise from constriction of the part by eschar, eg. respiratory impairment may follow circum- ferential burns of the chest,circulation to the distal part of an affected limb may be seriously impaired. Skin grafting is required except for small injuries.

Healing which is prolonged, occurs by secondary intention and there is no regeneration of sweat glands, hair follicles or sebaceous glands. Resultant scar tissue often limits movement of affected joints.

The extent of burns in adults is roughly estimated using the 'rule of nines' In adults, hypovolaemic shock usually develops when 15% of the surface area is affected.

Fatality is likely in adults with third degree burns if the surface area affected is added to the patient's age and the total is greater than 80.

Complications of burns Although burns affect the skin, when extensive, their sys ternic consequences can also be life-threatening or fatal.Dehydration and hypovolaemia.

These may occur in extensive burns when there is excessive leakage of water and plasma proteins from the damaged skin surface Shock.

Adverse effects and Toxicology of drug on skin :

Silver sulfadiazine is a medication used to prevent, manage, and treat burn wound in- fections.

It is a heavy metal topical agent with antibacterial properties. This activity reviews the indications, action, and contraindications for silver sulfadiazine as a valuable agent in preventing infection in burn patients.

This activity will highlight the mechanism of action, adverse event profile, and other key factor pertinent for members of the healthcare team in the care of patients with second and third-degree burns. Route of administration is Topical .

Medical professionals recommend its use once or twice daily, with reapplication as needed to prevent wound-sepsis in the treatment of burns.

Dermatologic reactions, including erythema multiforme, pruritis, skin discoloration, skin photosensitivity, rash, and Stevens-Johnson syndrome, have all been reported. Pa- tients who have previously experienced a rash in response to silver sulfadiazine should not use this medication as this can be a sign of an allergy.

It is unknown whether patients with sulfonamide allergies are at risk for cross-reaction to silver sulfadiazine, but product labeling indicates that those patients should avoid use if their previous reaction to sulfonamides has been severe.

Silver sulfadiazine is considered extremely safe, and overdose is uncommon; however, it is essential to remember that systemic absorption of the medication can occur and may be significant, especially when used near mucosal or ocular areas or when used ona large surface area.

In large amounts, propylene glycol is potentially toxic and, as mentioned previously, is found in many formulations of silver sulfadiazine.

Toxicity with these formulations has correlated with hyperosmolality, seizures, lactic acidosis, and respiratory depression.

Some researchers have found correlations between serum propylene glycol levels and osmolality changes, but these changes were attributed to a combination of medication usage and the physiologic changes of a severely burned state.

TREATMENT OF SKIN DISORDER:

Different diseases have different kinds of treatments, depending on what causes them. Therefore, there is no uniform treatment that works on every single skin disease .

Skin diseases can be treated with the application of certain medicines. These can be categorized as:

- Topical medications:

Topical medications mainly include:

- Antibacterials**:** Prevent infections. Examples are clindamycin, mupiro-cin, etc.
- Anthralin**:** Reduces inflammation and treats psoriasis-like conditions.

- Antifungal agents**:** Used to treat skin infections like ringworm, ath- lete's foot, etc.
- Benzoyl peroxide**:** Mainly used to treat acne. Examples are gels, creams, foams, etc. containing benzoyl peroxide.
- Corticosteroids**:**

- Oral medications:

Oral medications mainly include:

- Antibiotics**:** Commonly used antibiotics are erythromycin, tetracycline, dicloxacillin, etc.
- Antifungal agents**:** Oral antifungal medicines include fluconazole, itra- conazole, etc. these are used to treat fungal infections of skin and nails.
- Antiviral agents**:** Antiviral medicines like acyclovir, famciclovir, etc. treat skin conditions like herpes and shingles.
- Corticosteroids**:** These mainly include prednisone. It treats autoim- mune skin conditions like vasculitis and eczema.
- Immunosuppressants**:** These are used in the treatment of severe cases of psoriasis and eczema. Common examples of immunosuppressants are azathioprine and methotrexate.

INTRODUCTION TO TOXICOLOGY TESTING:

Toxicology testing is performed to identify the potential adverse effects a chemical poses to an individual and its surrounding environment. The different types of chemi- cals include active pharmaceutical ingredients, cosmetics ingredients, household, and industrial chemicals. An estimated number of 2000 new chemicals are produced for various applications; routine toxicology tests are conducted on increasing number of new chemicals on a daily basis to ensure its safety to potential consumer.

SKIN TOXICOLOGY :

deals with toxins that effect the integrity and functioning of the skin When a toxin reaches the skin it results in redness, pain, heat and swelling of the affected area. It mainly deals with toxins like pesticides and fungicide.

Skin toxicology testing

Toxicology testing , also known as safety assessment or toxicity testing is the process of determining the degree to which a substance of interest negatively impacts the nor- mal biological functions of an organism, given a certain exposure duration, route of exposure, and substance concentration. Toxicology skin tissue models are one of the most developed and understood in vitro engineered constructs and they have been widely utilized as an alternative testing tool by the cosmetics industry to replace the animal models. The native human skin is a large, complex organ containing multiple types of cells that are positioned relative to each other in highly-specific arrangement; it consists of anisotropic distribution of both cellular and extracellular matrix compo- nents .

The use of human-relevant skin tissue models enables more reliable and accurate cos- metics testing; different types of skin toxicology tests have been investigated and are well- documented by the test guidelines under the Organization for Economic Cooper- ation and Development (OECD) using the united nations globally harmonized system of classification and labelling of chemicals.

The four key OECD TG involving in vitro skin tissue models Corrosions:

- skin absorption
- skin corrosions
- skin irritation

(4) skin sensitization

- skin absorptions (OECDTG 428)

Skin absorption can be defined as the absorption of a test chemical by the skin through passive diffusion process when in direct contact to evaluate the systemic exposure and perform risk assessment. human or animal (for e.g. pig or rat) skin in the range of 200- 400 µm thickness is typically used for skin absorption studies.

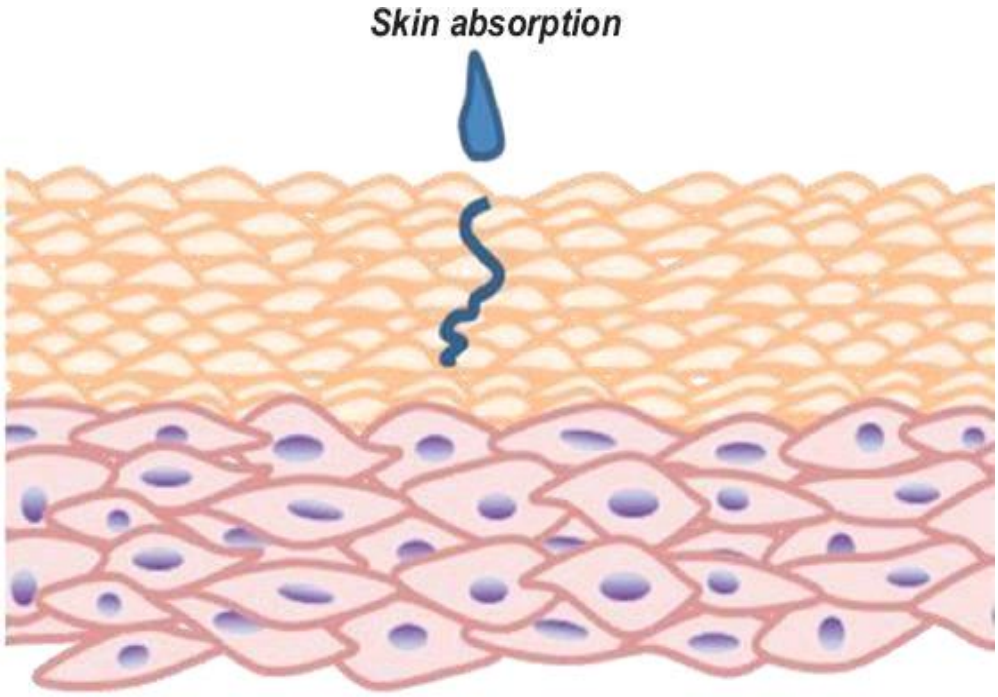

FIG NO:4

Preparation of the epidermal membranes is performed through heat separation (60°C for 1-2 min for human and pig skin) or chemical separation (2M sodium bromide for rat skin). It is important to perform in vitro skin integrity test to ensure an intact stratum corneum which is retained during skin preparation and a test substance, which may be radiolabeled, is applied to the surface of a skin sample separating the two chambers of

a diffusion cell. The application should mimic human exposure, normally 1-5 mg/cm2 of skin for a solid and up to 10 µl/cm2 for liquids. The chemical remains on the skin for 24 h at a constant temperature of 32±1°C to ensure constant passive diffusion of chemicals before removal by an appropriate cleaning procedure.

The receptor fluid is sampled at time points throughout the experiment and analyzed for the test chemicals and/or metabolites.

A key limitation is that the skin has been shown to metabolize some chemicals during percutaneous absorption, but the metabolites of test chemicals can still be quantified. Skin absorption relates to the degree of exposure to and possible effect of a substance which may enter the body through the skin. Human skin comes into contact with many agents intentionally and unintentionally. Skin absorption can occur from occupational, environmental, or consumer skin exposure to chemicals, cosmetics, or pharmaceuticalproducts.

- skin corrosion (OECD TG 431)

Skin corrosion can be defined as a cause of irreversible damage to the skin manifested as visible necrosis through the epidermis and into the dermis. .The theory underlying the skin corrosion test is

that corrosive substances can permeate the stratum via diffu- sion or erosion, and are cytotoxic to the base cell layers.The reconstructed human epi-dermis (RHE) is typically used for skin corrosion

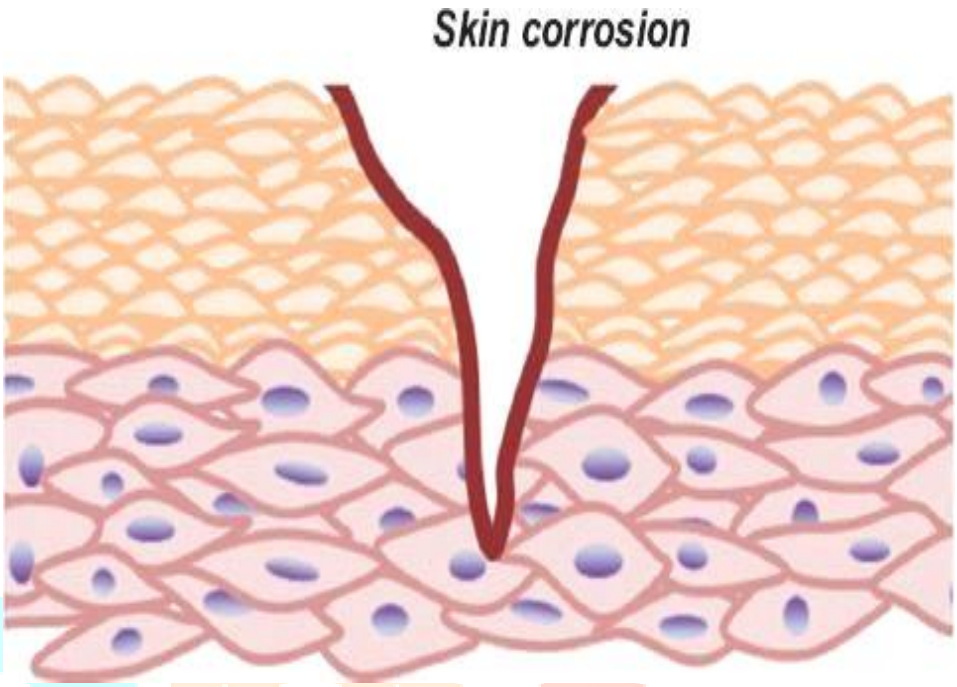

FIG NO:5

At least two tissue replicates should be used for each test chemical and controls for each exposure time; sufficient amount of test chemical should be applied to uniformly cover the epidermis surface (a minimum of 70 µL/cm2 or 30 mg/cm2) should be used. Con- current negative (NC) and positive controls (PC) should be used in each run to demon- strate that viability with NC, barrier function, and resulting tissue sensitivity with the PC of the tissues are within a defined historical acceptance range. Cell viability is meas- ured by enzymatic conversion of the vital dye MTT into a blue formazan salt that is quantitatively measured after extraction from tissues. Corrosive chemicals are identi- fied by their ability to decrease cell viability below-defined threshold levels (<50% vi- ability after 3 min exposure after 3 min exposure after 60 min of exposure – Class 1B and 1C), while chemicals that produce cell viabilities above the defined threshold level may be considered non-corrosive . A limitation of existing TG is that it does not allow the discriminating between skin corrosive sub-category 1B and sub-category 1C in ac- cordance with the UN GHS due to the limited set of identified in vivo corrosive sub- category 1C chemicals. The TG is currently only applicable to solids, liquids, semi- solids, and waxes; gases and aerosols have not been assessed yet in a validation study. It should also be noted that the test chemicals absorbing light in the same range as MTT formazan and test chemicals able to directly reduce the vital dye MTT may interfere with the tissue viability measurements and need the use of adopted controls for correc- tions. Hence, the use of adapted controls for corrections of interference measurementsis critical.

- Skin irritation(OECD TG 439)

can be defined as the cause of reversible damage (an inflammatory reaction that usually disappears after a few days) to the skin following the application of a test chemical There are two proposed mechanisms that lead to skin irritation, namely, the damage to the barrier function of the stratum corneum and the direct effect of irritants on the skincells.

At least three replicates should be used for each test chemical and for the controls (PC and NC) in each run and sufficient amount of test chemical (26-83 µL/cm2 or mg/cm2 should be applied to uniformly cover the epidermis surface The in vitro RHE test sys- tem measure the cell/tissue damage using cell viability as readout. Cell viability in RHE

models is measured by the enzymatic conversion of the vital dye MTT into a blue form- azan salt that is quantitatively measured after extraction from tissues.

Irritant chemicals are identified by their ability to decrease cell viability below-defined threshold levels Depending on the regulatory framework and applicability of the TG, chemicals that produce cell viabilities above the defined threshold level may be consid- ered non-irritants .A limitation of existing TG is that it does not allow the classification of chemicals to the optional UN GHS category 3 (mild irritants). The TG is applicable to solids, liquids, semi-solids, and waxes; gases and aerosols have not been assessed yet in a validation study. It should also be noted that the highly-colored chemicals may interfere with the cell viability measurements and need the use of adopted controls for corrections. Hence, the use of adapted controls for corrections of interference measure- ments is critical.

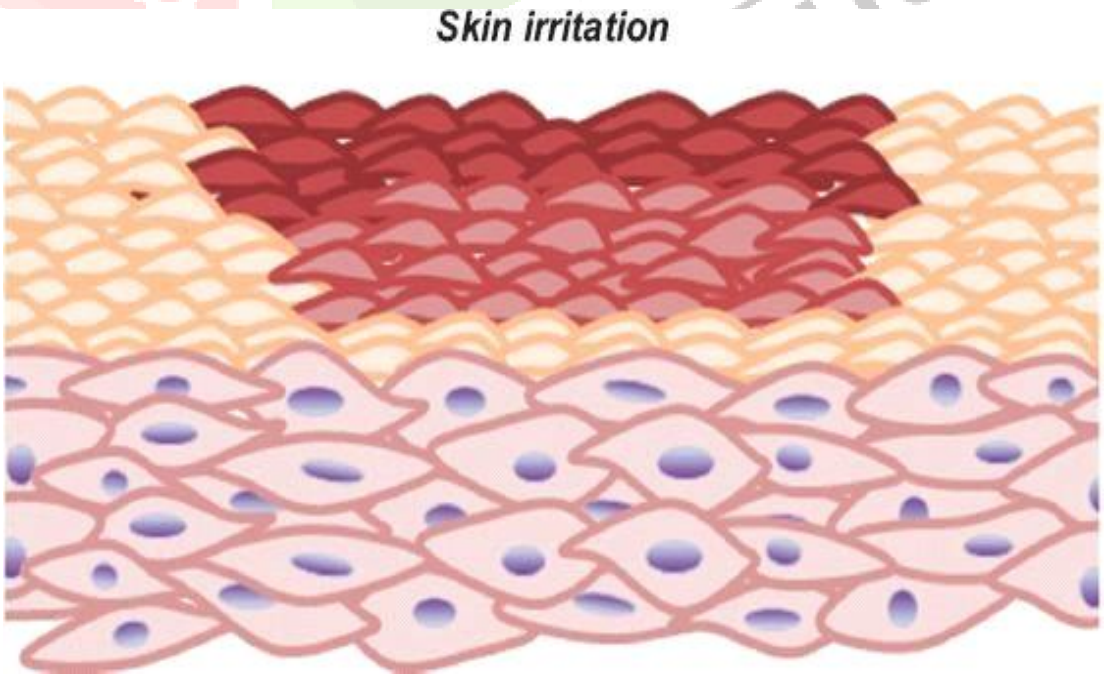

FIG NO:6

- skin sensitization (OECDT TG 442D)

It is defined as an allergic response to a chemical following skin contact as defined by UN GHS. Follow the principal of A sensitizer can upregulate the luciferase activity and allows quantitative measurement of luciferase gene induction. An adverse outcome pathway (AOP) has been developed to represent the chemical and biological pathways

involved in skin sensitization, and it progresses from the molecular initiating event through the intermediate events and ultimately to the unfavourable health impact

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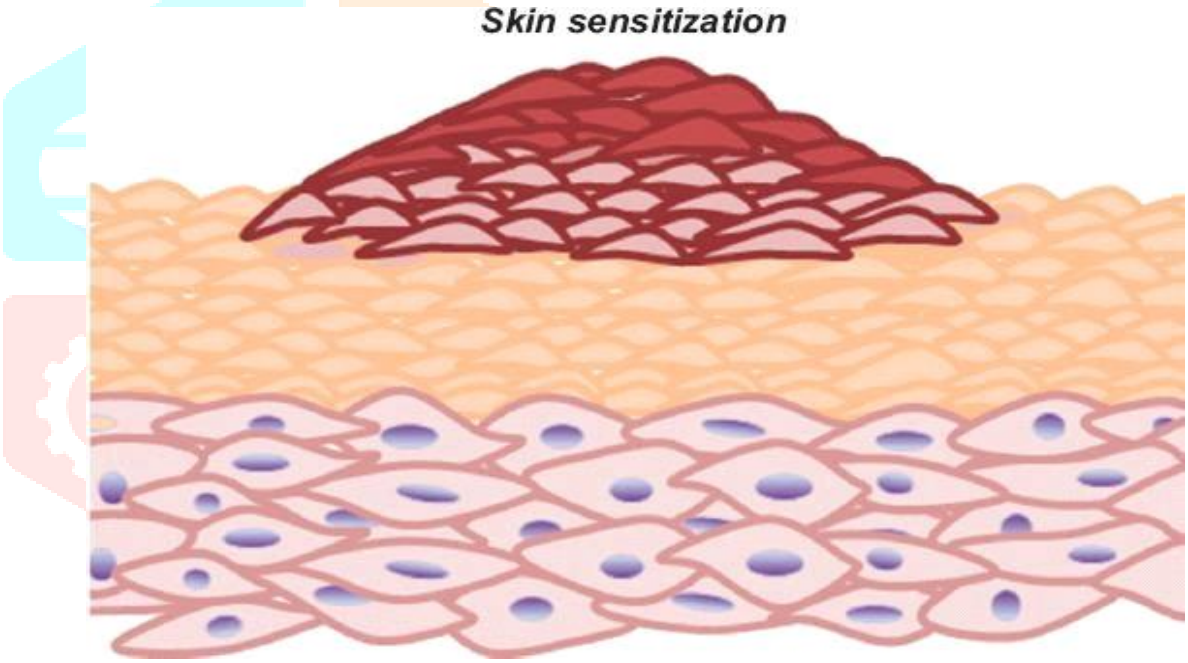

FIG NO:7

- Skin sensitization begins from the molecular initiating event through covalent binding of electrophilic substances to nucleophilic centers in skin proteins to, specific cell signaling pathways such as antioxidant/electrophile response ele- ment (ARE)-dependent pathways to,activation of dendritic cells, and finally T- cell proliferatio The TG addresses the 2nd key event whereby the dissociated transcription factor nuclear factor-erythroid 2-related factor 2 can activate the ARE-dependent genes. The only ***in vitro*** validated luciferase test method in- volves the use of KeratinoSens™ (RHE) which is made up of an immortalized adherent cell line derived from HaCaT human keratinocytes stably transfected with a selectable plasmid

and the luciferase test method allows quantitative measurement of luciferase gene induction following exposure to electrophilic test substances. Three replicates are used for the luciferase activity measure- ments, and one parallel replicate used for the cell viability assay.

- Test chemicals are considered positive if they induce a statistically significant induction of luciferase activity above a given threshold (i.e., 50% increase) be- low a defined concentration which does not significantly affect cell viability (i.e., below 1000 µm and at a concentration at which the cellular viability is above 70%). As this testing guideline only focuses on the 2nd key event of the skin sensitization AOP, the results from the test are unlikely to be sufficient when used on its own. Hence, combining them with other complementary in- formation addressing other key events of skin sensitization AOP would give more accurate predictive outcomes.
- Although most of the current validated ***in vitro*** skin models are RHEs, it has been shown that the presence of fibroblasts increases the resistance of keratino- cytes to toxic chemicals. These findings indicate that the use of full-thickness (FT) skin models would generate more meaningful data for kitoxicology test- ing. Furthermore, the use of FT skin models in skin absorption studies has also generated good data reproducibility Hence, the use of 3D bioprinting technol- ogy would enable the fabrication of more complex and biomimetic 3D FT skin models in a standardized manner that can potentially improve the reliability and accuracy of different skin toxicology tests.

CONCLUSION

- skin toxicology is current challenge for public Health protection. it is largest organ of body In these minor project we studied that many Disorder act on skin and it was treat by various method.
- In skin toxicolgy it Focus the toxin that effect the integrity and functioning of skin. A poison that enter the skin causes affected area to become red, Painful, hot & swollen .It mostly addresses contaminant like fungicide & insecticides.
- Skin toxicolgy is studied by various vitro skin tissue model as per OECD TG Guidelines.
- The global market for in vitro toxicology testing market has been estimated to be-USD 13 billion in 2016, and it is projected to reach USD 20.8 billion by theend of 2021.

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