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CHARACTERIZATION OF INDOOR DUST-DERIVED TRACE ELEMENTS AND ORGANIC CONTAMINANTS' IMPACT ON HUMAN LUNG CELLS

DISSERTATION

Presented in Partial Fulfillment of the Requirements

for the Degree Doctor of Philosophy in the

Graduate School of Texas Southern University

By

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By

Ayat Ali, Ph.D.

Texas Southern University, 2021

Professor Shishir Shishodia, Advisor

These days, people spend most of their time indoors. Therefore, indoor dust can be one of the main pathways of exposure to toxic contaminants. Indoor dust is a complex mixture of particles with organic and inorganic pollutants, such as heavy metals, smoke residues, flame retardants, pesticides, polycyclic aromatic hydrocarbons, and plasticizers. Depending on the size and the composition, indoor dust has been associated with different toxicological effects because of its ability to modify several biological activities, activate different cellular pathways, and induce DNA adducts. These alterations can lead to respiratory diseases like asthma, chronic obstructive pulmonary disease, lung fibrosis and cancer.

This study aimed to determine the effect of the indoor dust (Trace Elements Indoor Dust and Organic Contaminants House Dust) on cell viability, cytotoxicity, cellular death mechanism, cellular oxidative stress, inflammasome activation, and Mitogen-Activated Protein Kinase pathway activation in normal human bronchial epithelial cells (BEAS-2B) after exposure to different dust concentrations (10, 25, 50, 75, 100, 250, and 500 µg/ml).

The research covers the proliferation of normal human bronchial epithelial cells using 3-(4,5 dimethyl-2-thiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Viability and apoptosis were measured in BEAS-2B cells by the Triplex assay. Cytotoxicity was measured using LDH-Glo cytotoxicity assay. Reactive oxygen species (ROS) were measured by the dichlorofluorescein (DCFH) oxidation assay and the ROS-Glo-H_2O_2 assay. For detection of inflammation, Inflammasome-Glo Caspase-1 assay was used. MAPK protein levels (JNK, ERK1/2, and p38) and antioxidant enzymes' levels (Superoxide Dismutase-1, Superoxide Dismutase-2, Catalase, and Glutathione Peroxidase) were determined using western blotting.

Our findings indicate that indoor dust exposure results in cell growth suppression, cell cytotoxicity, ROS overproduction, antioxidant enzymes activation, activation of the inflammatory response, and MAPK pathway activation in normal lung cells, which together cause apoptotic, necrotic, and pyroptotic cell death, and that may pose a risk for respiratory disorders and airway injury.

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LIST OF ABBREVIATIONS

Ac-YVAD-CHO	N-acetyl-L-tyrosyl-L-valyl-N-[(1S)-2-carboxyl-1-formylethyl] -L- alaninamide
APEs	Alkylphenols And Their Ethoxylates
BBP	Bis Benzyl Butyl-Phthalate
BCA	Bicinchoninic Acid
BEAS-2B	Virus Transformed Human Lung Epithelial Cells
BEH-TEBP	Bis(2-Ethylhexyl) Tetra-Bromo-Phthalate
BPE	Bovine Pituitary Extract
CAT	Catalase
DBP	Dibutyl Phthalate
DCFH	Dichlorofluorescin
DDT	Dichloro-Diphenyl-Trichloroethane
DEHP	(2-Ethylhexyl) Phthalate
DMSO	Dimethyl Sulfoxide
EH-TBB	2-Ethylhexyl) 2,3,4,5-Tetrabromobenzoate
EPA	Environmental Protection Agency
ERK	Extracellular Signal-Regulated Protein Kinase
FBS	Phosphate Buffer Saline
FRs	Flame Retardants
GF-AFC	Glycylphenylalanyl-Aminofluoroumarin
GPx	Glutathione Peroxidase
H_2DCFDA	2′ ,7′ -Dichlorofluorescein Diacetate

ip-PDPP	Isopropyl-Phenyl Diphenyl Phosphate
JNK	C-Jun N-Terminal Kinase
LDH	Lactate Dehydrogenase
MAPK	Mitogen Activated Protein Kinase
MEKK1	Mitogen-Activated Protein Kinase Kinase Kinase 1
MG132	Carbobenzoxyl-Leucinyl-Leucinyl-Leucinal Proteasome Inhibitor
MKK4	Mitogen-Activated Protein Kinase Kinase 4
MKK7	Mitogen-Activated Protein Kinase Kinase 7
MKP	MAPK Phosphatases
MTT	3-(4,5-Dimethylthiazole-2-Yl)-2,5-Diphenyl Tetrazolium Bromide
Nfκb	Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells
NIST	National Institute of Standards and Technology
NLRP3	NLR Family Pyrin Domain Containing 3
OCPs	Organochlorine Pesticides
PAEs	Phthalic Acid Esters
PAHs	Polycyclic Aromatic Hydrocarbons
PBB	Polybrominated Biphenyls
PBDEs	Polybrominated Diphenyl Ethers
PBS	Phosphate Buffer Saline
PCBs	Polychlorinated Biphenyls
PFRs	Organophosphate Flame Retardants
PM	Particulate Matter
PPAR-Gamma	Peroxisome Proliferator-Activated Receptor Gamma

RIPA	Radioimmunoprecipitation Assay
ROS	Reactive Oxygen Species
SDS-PAGE	Sodium Dodecyl Sulfate-Polyacrylamide Gel Electrophoresis
SOD1	Superoxide Dismutase-1
SOD2	Superoxide Dismutase-2
SRM	Standard Reference Material
TBS	Tris-Buffered Saline Solution
TBST	Tris-Buffered Saline Buffer Containing 0.1% Tween-20
TCEP	Tris (2-Chloroethyl) Phosphate
TCIPP	Tris (Chloropropyl) Phosphate
TDCIPP	Tris (1,3-Dichloro-2-Propyl) Phosphate
TPHP	Triphenyl Phosphate

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CHAPTER 1
INTRODUCTION

Much attention has been paid to investigating, analyzing, and controlling outdoor air pollution. As a consequence, air pollution is usually thought to be only an outdoor phenomenon. However, indoor air can be more polluted (USEPA, 1987). The United States Environmental Protection Agency has classified indoor pollution as a very import risk to human health (Health Canada, 1989). In the previous few years, indoor air pollution has caused growing concern (McCormack et al., 2008) because it considered the main pathway for human exposure to toxic contaminants in re-suspended and settled dust (Mohmand et al., 2015; Morawska, 2004; Schripp et al., 2008), such as polycyclic aromatic hydrocarbons (PAHs), organophosphorus flame retardants, polybrominated diphenyl ethers (PBDEs), plasticizers, parabens, pesticides, bisphenols, and other chemicals that impacting human health (Butte & Heinzow, 2002; Laborie et al., 2016; Larsson et al., 2017; Liao et al., 2012; Loganathan & Kannan, 2011; Tran et al., 2016; Wang et al., 2012). These compounds persisted and accumulated in house dust, as they are not exposed to the same outdoor factors, such as sunlight, microbial degradation, high temperature, moisture fluctuation, and overall weathering impacts (Paustenbach et al., 1997).

Indoor dust is a heterogeneous combination of particles with a variety of inorganic and organic contaminants. The percentage of inorganic and organic matter in house dust may differ extensively (Butte & Heinzow, 2002; USEPA, 1997; VDI, 2001). It can trap,

accumulate, and preserve contaminants (Cizdziel & Hodge, 2000), so it can be used as an archive for indoor pollution (Butte & Walker, 1994).

The composition of indoor dust can vary significantly between rooms in a specified house and between houses and locations (Lioy et al., 2002). Several seasonal and environmental factors greatly affect the composition of indoor dust, these factors including the surroundings, air exchange and ventilation, house age, conditions of building materials, cleaning habits, type of furniture and carpets, in addition to the activities of the occupants (Butte & Walker, 1994).

In addition to the differences in dust chemical composition, the particle shape, size, and density also vary greatly (Lewis et al., 1999; Que Hee et al., 1985). The size of the dust particles ranges from below 1 micron to at least 100 microns. They will slowly settle under the influence of gravity and may become airborne due to their origin, physical characteristics, and environmental conditions (IUPAC, 1990).

Individuals are continuously exposed to dust particles through different pathways, which are inhalation, skin contact, and ingestion (Blanchard et al., 2014; Mercier et al., 2011; Weschlera & Nazaroff, 2008). Indoor activities, such as cleaning, vacuuming, walking, or playing, can cause dust suspension or re-suspension, leading to dust inhalation (Thatcher & Layton, 1995). Whether the particles are deposited in the head or the lung, they may cause local or systemic harm to the body. Particles that last for a long time have increased ability to cause diseases. Soluble particles deposited in any area can dissolve and release substances that may be harmful to the human body and can be absorbed from any part of the respiratory tract, so it is of little importance for the deposition site and aerodynamic diameter of soluble particles. However, the deposition site of insoluble

particles in the respiratory system is critical, this implies that the particle's aerodynamic properties, shape, dimensions of the airways, and breathing patterns are relevant. (Hinds, 1982; Parkes, 1994; Vincent, 1995).

Several studies revealed that heavy metals and organic pollutants in indoor dust were certainly associated with human diseases (Betts, 2015; He et al., 2015; Kolarik et al., 2008; Meeker & Stapleton, 2010) due to their persistence in the environment and their adverse impacts (Yu et al., 2014). These impacts include immunological, respiratory, cardiovascular, reproductive, and central nervous system problems, allergies, skin and mucous membrane irritation, and cancer (Ezzati & Kammen, 2001; Gereda et al., 2002; Maroni et al., 1995).

The first physical barrier against inhaled particles and environmental factors is the respiratory epithelium, which cover the surface of the airways and alveoli. It is work as an essential factor of the inflammatory defense mechanism as it develops various pro-inflammatory molecules after exposure to damaging compounds (Cunningham & Mahone, 2002; Takizawa et al., 1999). Hence, lung epithelial cell cultures are commonly used in in vitro studies to study the possible detrimental effects of particulate matter and other inhaling contaminants (Ahktar et al., 2010; Becker et al., 2005; Ortgiesen et al., 2000; Salonen et al., 2004; Veronesi et al., 2002; Zarcone et al., 2016). Most of these studies used immortalized respiratory cell lines. Besides that, studying primary cell cultures is also important as they more closely resemble in vivo conditions.

Previous studies demonstrated that exposure to the particulate matter could lead to increased oxidative damage, DNA breaks, DNA adducts (Bai et al., 2001; Lepers et al., 2013; Sevastyanova et al., 2007), and cell death (Bai et al., 2001; Billet et al., 2007;

Danielsen et al., 2008), as well as an increased frequency of mutations and genetic rearrangements (Claxton et al., 2004; Du Four et al., 2005; Motta et al., 2004; Saint-Georges et al., 2009). Two distinct death pathways can occur in cells exposed to PM (de Kok et al., 2006; Schwarze et al., 2006), which are necrosis and apoptosis (programmed cell death). In addition to the PM's chemical properties, the exposure dose is also important in triggering the specific death mechanism. (Nel et al., 2001). The same chemical induces an apoptotic pathway at low doses can result in a necrotic pathway activation at higher doses (Elmore, 2007).

Reactive oxygen species are chemically reactive molecules commonly found within the cells during normal cellular activation and serve multiple purposes, including cell differentiation, controlling gene expression, and cytokine responsiveness. It has been identified as a main mechanism of cytotoxicity triggered by particulate matter (Akhtar et al., 2010; Deng et al., 2013). Adverse biological effects can occur due to the imbalance between the production of ROS and the antioxidant defenses (Limon-Pacheco & Gonsebatt, 2008). Several studies have shown that the pariculate matter chemical contaminants could induce DNA damage, inflammation, oxidative stress, fibrosis, and cell cytotoxicity (Deng et al., 2013; Li et al., 2008; Schwarze et al., 2006; Tao et al., 2003; Yi et al., 2014; Zorov et al., 2014). It was found that ROS production is directly linked to the effect of transition metals (DiStefano et al., 2009), while organic compounds indirectly affect ROS generation (Michael et al., 2013).

In toxicological and environmental analyses, standard reference materials (SRMs) are frequently utilized as scale or control samples. The SRMs offered by the National

Institute of Standards and Technology (NIST) are related to the most trustworthy materials used in toxicological research (Jacobsen et al., 2008; Masi, 2008; May et al., 1992). The use of standard reference materials over raw samples has various advantages, including well-documented sample composition and the ability to compare results from different studies.

Aims and Objectives

This study aims to:

1. Determine the effect of indoor dust on cell viability, cytotoxicity, and cellular death mechanism (caspases 3/7 activation) in normal human bronchial epithelial cells (BEAS-2B).
2. Determine the effect of indoor dust on induction of oxidative stress by measuring the generation of reactive oxygen species (ROS) and the protein expression of antioxidant enzymes (superoxide dismutase, catalase, and glutathione peroxidase) in normal human bronchial epithelial cells (BEAS-2B).
3. Determine if the indoor dust exposure activates Inflammasome-Caspase 1 in normal human bronchial epithelial cells (BEAS-2B).
4. Determine if the indoor dust exposure activates the Mitogen-Activated Protein Kinases signaling pathway (JNK, ERK1/2, and p38) in normal human bronchial epithelial cells (BEAS-2B).

CHAPTER 2

LITERARY REVIEW

Origin and Exposure Routes of Indoor Dust

Indoor dust is a diverse mix of materials from many sources, such as soil particles, clothing, particulate matters, hair, skin particles, fibers, pollen, arthropods, ash, soot, animal fur and hair, allergens, cooking residues, building materials, molds, bacteria, and viruses (Paustenbach et al., 1997).

Inhalation, ingestion, and dermal adsorption are the routes of exposure to suspended indoor dust and related contaminants. These contaminants are subjected to variabilities, such as space and time variabilities, responsible for resulting heterogenicity in dust composition (Figure-1).

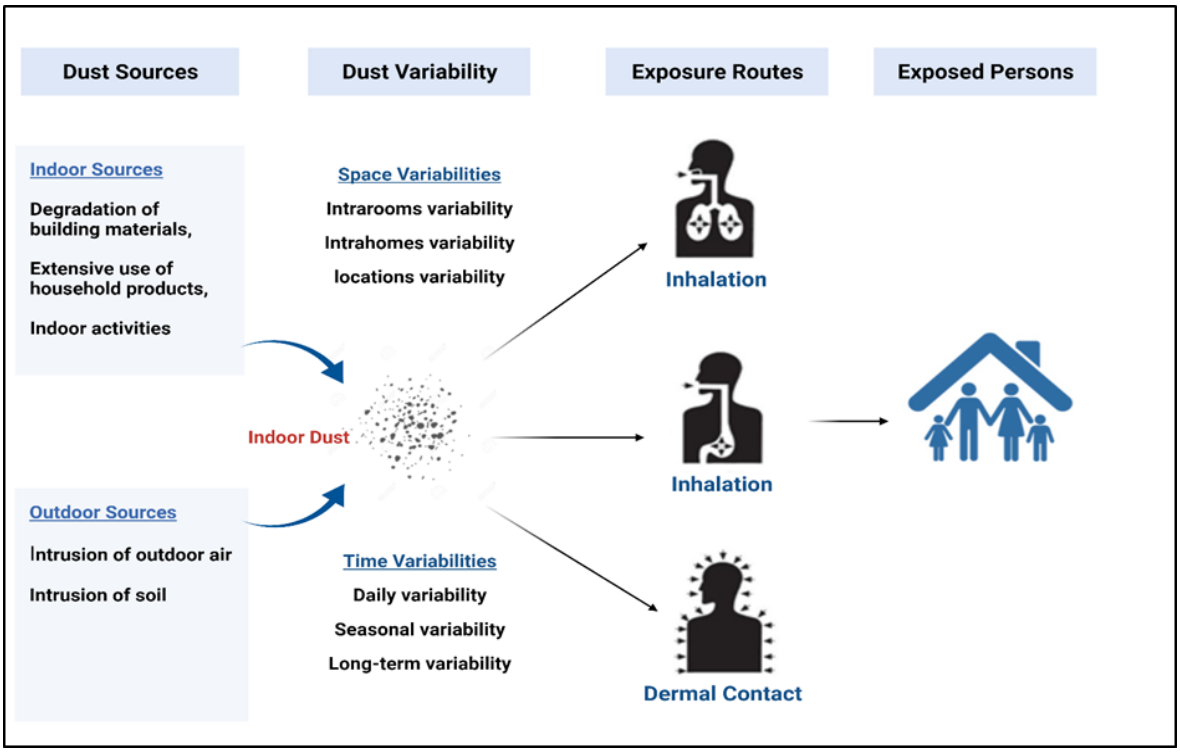


Figure 1: Indoor dust variabilities and exposure routes.

Inhalation

Indoor activities, like playing, cleaning, vacuuming, or even walking in a room, can cause the suspension and resuspension of the dust particles and lead to dust inhalation (Thatcher & Layton, 1995). The estimation of adults' dust inhalation is 0.81 mg/day, while children can inhale about 0.15 - 0.34 mg of dust daily (Hawley, 1985). Generally, the upper respiratory tract can trap any dust particles larger than ten micrometers. In comparison, finer particles (< 2.5 μm) can deeply enter the respiratory system and are less likely to be eliminated (Morawska & Salthammer, 2003). These particles contain high concentrations of polycyclic aromatic hydrocarbons, and they can cause high toxicity risk to the exposed persons (Lewis et al., 1999).

Non-Dietary Ingestion

Children who put playing objects like toys, and even their hands into their mouth, are generally thought to accidentally ingest dust particles on the objects or their skin (Lewis et al., 1999). Via this route of exposure, adults can ingest 0.56 mg of dust daily, while children ingest 50 to 100 mg/day (Hawley, 1985). Some children might ingest about 10 g of dust and soil daily because of eating non-food items (pica behavior) (Calabrese & Stanek, 1992).

Dermal Contact

Contact with dust accumulated on furniture, floors, and other items may cause dermal adsorption of dust. The skin mostly retains dust particles less than 100-200 μm in diameter (Lewis et al., 1999). About 28 mg and 51 mg of indoor dust can be adsorbed daily to children's and adults' hands, respectively (Hawley, 1985). Such exposure route is thought to be less critical in a non-occupational environment than inhalation and ingestion (Chuang et al., 1999).

Characteristics of Dust Particles

The aerodynamic diameter of particles becomes the determinant for the time a particle remains airborne, if it is to be inhaled, and where the dust will be deposited in the respiratory system. In addition, the quantity of dust in the air will determine the quantity of deposited dust in the critical site. Wherever they are deposited (in the upper respiratory tracts or in the lung), dust particles can cause a different degree of harm locally or elsewhere in the body, depending on the position where they have been deposited. While some particles may have lower chances of causing harmful effects, particles that remain for longer times have increased chances of causing diseases. So, the evaluation and control

of inhaled dust particles are very important. Several factors can determine the fate of insoluble dust particles deposition, such as their aerodynamic diameter, their shapes, the dimensions of the airways, and the breathing patterns. The soluble and very soluble dust particles can be dissolved and readily absorbed from any part of the respiratory tract and release potentially toxic materials that are harmful to the body (Hinds, 1982; Parkes, 1994; Vincent, 1995). Therefore, the deposition site and the aerodynamic diameter of very soluble particles are less important (Figure-2).

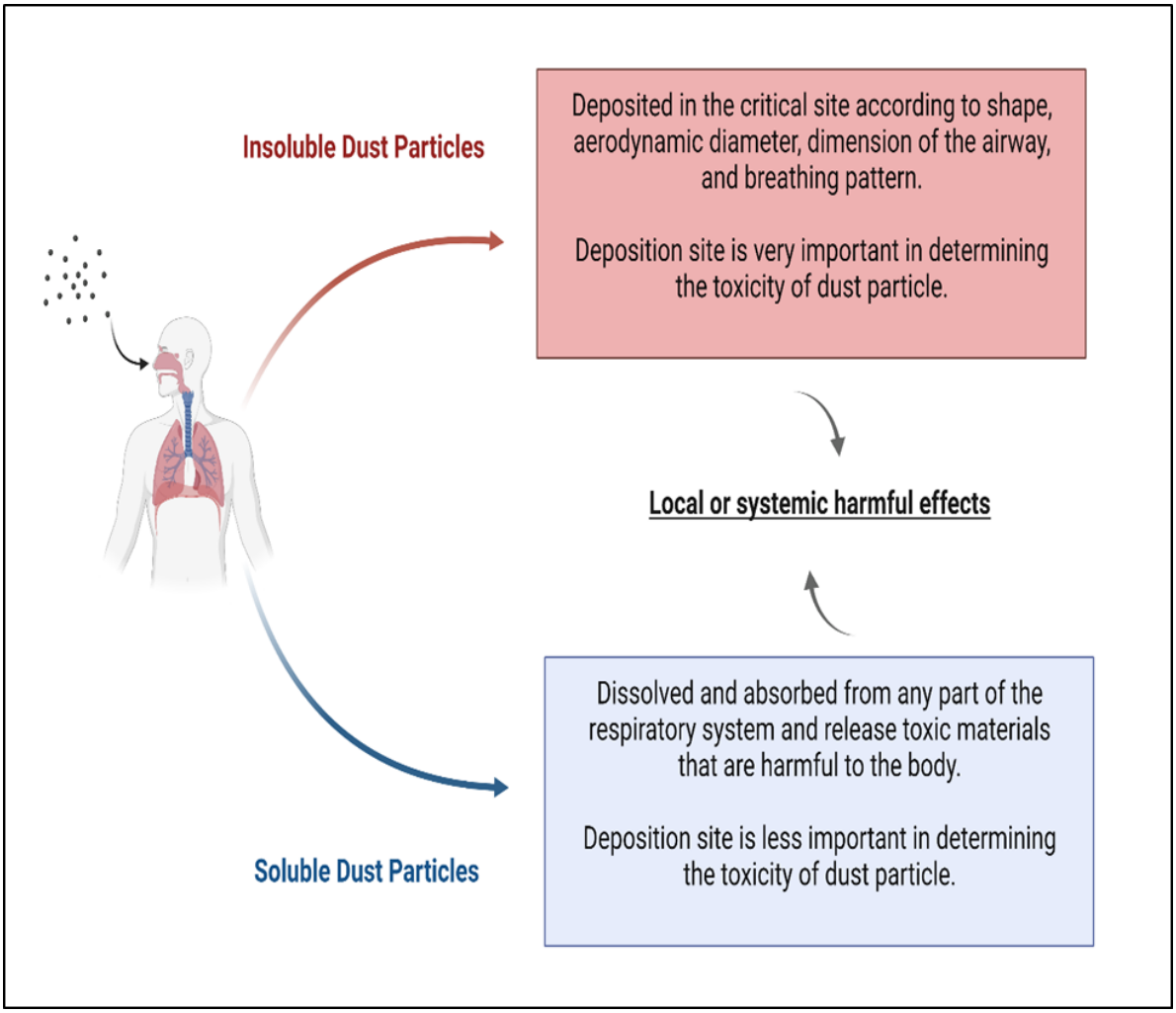


Figure 2: Characteristics of dust particles

Indoor Dust Contaminants

There are many contaminants in indoor dust that are come from different sources. They are able to metabolize and react with each other and with the human body causing serious effects. They are classified into two major groups (chemical and biological contaminants), as shown in Figure-3.

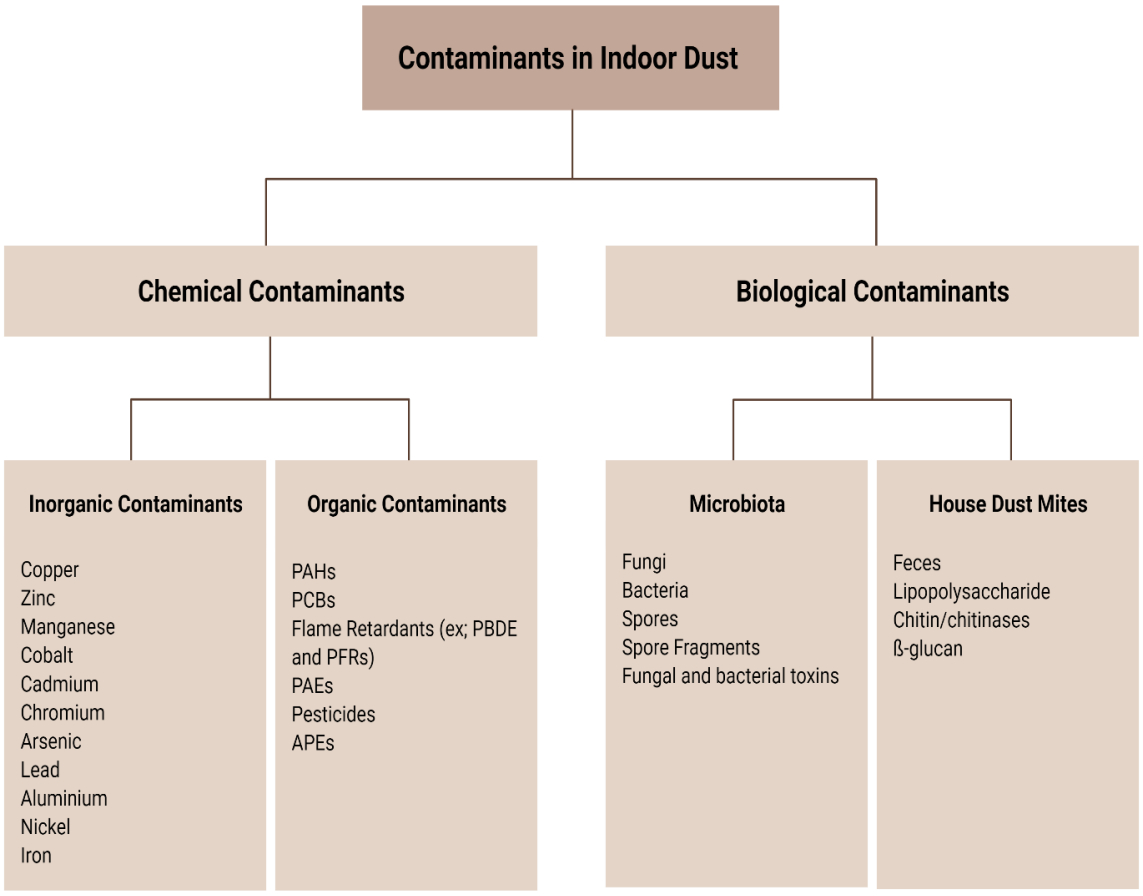


Figure 3: Indoor dust contaminants

Chemical Contaminants in Indoor Dust

1- Inorganic Contaminants

Copper, Zinc, Manganese, and Cobalt at trace levels can act as micronutrients for human and animals' growth, while cadmium, chromium, and arsenic act as carcinogens. Anions at low concentrations are beneficial to the human body; they help renew and promote better functioning of cells and body parts, thus improving body health (Trichopoulos et al., 1997).

The non-biodegradable and harmful nature of trace metals in the environment is a significant area of concern, particularly if their accumulation levels in the body are higher than those needed (Kong et al., 2011). Trace metals accumulation in human organs and body tissues can act as promoters, stimulants, and cofactors, affecting the central nervous system and can lead to trace metal diseases (Mass et al., 2010).

Inorganic pollutants in indoor dust have a human toxicity risk, especially young children, as revealed by the researchers' reports (Akhter & Madany, 1993; Chattopadhyay et al., 2003; Jaradat et al., 2004; Rashed, 2008; Latif et al., 2009; Rasmussen et al., 2001; Yaghi & Abdul-Wahab, 2004). Several studies have been made to determine the existence of these pollutants in different environmental media such as road dust, food, and water (Asante et al., 2012; Charlesworth et al., 2003; Duong & Lee, 2009; Duzgoren-Aydin et al., 2006; Gunawardana et al., 2012; Khan et al., 2008; Leung et al., 2008; Okonkwo et al., 2006; Polat & Erdogan, 2007; Radwan & Salama, 2005; Rashed, 2008; Sekabira et al., 2010; Sutherland 2003; Zheng et al., 2010).

The International Agency for Research on Cancer (IARC) classified zinc, aluminium, nickel, cobalt, iron, and copper as carcinogenic elements, while lead, arsenic,

cadmium, and chromium have been classified as carcinogenic and non-carcinogenic. Smaller volumes of trace metals like Zinc and Copper are harmless, while some like cadmium and lead, even at lower volumes, are extremely toxic and can interfere with gene expression, DNA replication, and DNA repair by competing with nuclear uptake, homeostasis, and the function of essential metal ions (Chattopadhyay et al., 2003; Gomaa et al., 2002; Gulson et al., 2003; Menzie et al., 2009; Myers & Davidson, 2000; Whicker et al., 1997). They are able to accumulate in the body's fatty tissues, and they might be concentrated in the circulatory system causing damage to the central nervous system and affecting the normal functions of internal organs (Bocca et al., 2004; Waisberg et al., 2003). In addition, they can promote several diseases such as respiratory diseases, cardiovascular diseases, cancer (Dockery & Pope, 1996; Sanborn et al., 2002; Tchounwou et al., 2003; Willers et al., 2005), and slow development (Faiz et al., 2009; Turner & Hefzi, 2010).

The sources of metal-laden indoor dust are vehicle pollution, polluted soil, the fine particulate matter created by paint, and road surface degradation (Hunt et al., 1992). The daily burning of fuel for cooking is a major source of heavy metals in households (Hassan, 2000).

Wall paints are considered a very important source of heavy metals in the dust. Green paint is associated with high concentrations of copper, purple paint is associated with high zinc and lead concentrations, while yellow paint is related to high concentrations of cadmium, copper, lead, and zinc (Chattopadhyay et al., 2003; Tong & Lam, 2000).
The proportion of fungi, molds, and other organic materials that have the potential to absorb metals, is also likely to affect total concentrations of metals in indoor dust (Rasmussen et al., 2001).

2- Organic Contaminants

Polycyclic Aromatic Hydrocarbons (PAHs)

Due to incomplete combustion, PAHs are produced, which are a group of carbon-based compounds made up of fused aromatic rings organized in a linear, angular, or clustered pattern. They are present as complex mixtures rather than single compounds. Indoor and outdoor sources, such as cigarette smoke, appliances, fireplaces, grilled or smoked foods, and vehicle exhaust considered the main sources of PAHs exposure (Agency for Toxic Substances and Disease Registry, 1995).

PAHs has been found in many places in the surrounding environments, including indoor dust, blood, air, and urine (Beyea et al., 2006; Burstyn et al., 2000; Chuang et al., 1995, 1999; Dai et al., 2004; Gevao et al., 2007; Jacob & Seidel, 2002; Kriek et al., 1998; Lewis et al., 1999; Maertens et al., 2004, 2008; Murkerjee et al., 1997; Onyemauwa et al., 2009; Sobus et al., 2009; Pleil et al., 2004; Rudel et al., 2003; Tjoe Ny et al., 1993; Wilson et al., 2003). PAH concentrations in indoor dust can give a long-term prediction of exposure to indoor PAH since PAHs are able to accumulate in carpets over the years (Roberts et al., 2009).

Indoor dust in urban homes was found to have higher concentrations of PAHs than in rural homes (Chuang et al., 1999). Also, Smoking homes have higher PAHs concentrations than non-smoking homes (Maertens et al., 2004). Other factors as well can affect PAHs concentrations in indoor dust, such as seasonal variations (Murkerjee et al., 1997) and cleaning frequency (Maertens et al., 2008).

Benzo(a)pyrene is identified as a human carcinogen, and several other polycyclic aromatic hydrocarbons are identified as class B2 probable carcinogens (IARC, 2004).

Polycyclic aromatic hydrocarbons are major toxic components that have been found in higher levels in indoor dust (Chuang et al., 1995; Chuang et al., 1999; Fromme et al., 2004; Maertens et al., 2004; Maertens et al., 2008; Mahler et al., 2010; Mannino & Orecchio, 2008; Mukerjee et al., 1997).

Harmful health effects may result due to unintentional exposure to PAHs, depending on their nature, level, and exposure periods (IARC, 2010), such as respiratory diseases (Whitehead et al., 2011a, b), nervous system tumors, and leukemia (Rengarajan et al., 2015; Sánchez-Guerra & Quintanilla-Vegal, 2013), lung, bladder and skin cancers (Boffetta et al., 1997; Perera et al., 2002). Furthermore, IQ deficiencies, cognitive developmental delays, and reduced gestational size have all been linked to in utero exposure to PAHs (Choi et al., 2008; Jedrychowski et al., 2005; Miller et al., 2004; Perera et al., 2006, Perera et al., 2009).

Polychlorinated Biphenyls (PCBs)

They are 209 lipophilic heat-resistant compounds mainly manufactured and used between the 1930s and 1970s. PCBs are considered to be persistent and bioaccumulative contaminants. They have a global distribution in the environment due to their extensive application, mobility, and chemical stability. Several health effects have been associated with human exposure to PCBs, such as childhood leukemia (Ward et al., 2009), neuro-behaving changes (Faroon et al., 2000), and decreased insulin synthesis (Jensen et al., 2014). While in transformers and condensers, PCBs were mainly used as coolants and insulants; about 10% of US PCBs applications included materials like plasticizers in sealants for buildings construction (Davies & Delistraty, 2016). These materials are important sources of PCBs found in indoor dust and soils (Herrick et al., 2007; Knobeloch

et al., 2012; Kohler et al., 2005; Orloff et al., 2003; Priha et al., 2005; Wang et al., 2013). For example, wood floor finishes are important sources for high-level PCBs in indoor dust (Rudel et al., 2008).

Because children have comparatively high rates of soil and dust ingestion, the existence of PCBs in these sources is of concern (USEPA., 2008). Several studies have revealed that following soil and dust ingestion, significant amounts of sorbed PCBs become desorbed and free for uptake into the circulation (bioaccessible) and for delivery from the circulatory system to the target organs (bioavailable) (Ertl & Butte, 2012; Feidt et al., 2013; Fournier et al., 2012; Fries et al., 1989; Hack & Selenka, 1996; Oomen et al., 2000; Van Eijkeren et al., 2006).

Flame Retardants (FRs)

They are additives utilized in consumer products and building materials. Over time, they can leach into the environment and accumulate in dust and on other surfaces because they are not chemically bound to these materials. Many of them are abundant in indoor dust because of their high octanol-air partitioning coefficients (Dodson et al., 2012; Harrad et al., 2009; Johnson-Restrepo & Kannan, 2009; Schecter et al., 2005; Stapleton et al., 2012). Ingestion of indoor dust is one of the most common ways for children and toddlers to be exposed to flame retardants, as revealed by several studies (Johnson et al., 2010; Stapleton et al., 2012).

- **Polybrominated Diphenyl Ethers Flame Retardant (PBDE)**

Flame retardants utilized commercially in household products, like foam furniture padding, electronics, and plastics, are called polybrominated diphenyl ethers (Frederiksen

et al., 2009; Johnson-Restrepo & Kannan, 2009). Human exposures to PBDE increased around two folds from the mid-1970s to the mid-2000s (Schecter et al., 2005; Sjodin et al., 2004). Following manufacturing restrictions because of concern about extensive exposure, toxicities, and persistence, some studies had initially stated subsequent decreases concentrations of PBDEs in human serum in the US and other nations (Guo et al., 2016; Kim et al., 2018). While other studies revealed that human serum concentrations of some congeners have stabilized or increased from 2011–2015 (Hurley et al., 2017; Parry et al., 2018), suggesting persistent exposure.

Furthermore, due to their stability and lipophilicity, these compounds continue to be abundant in many consumer products, the human body, the atmosphere, and the food supply (Hammel et al., 2017; Watkins et al., 2011; Xu et al., 2016). Exposures can also remain elevated in some developed countries where development and use regulations are less strict (Jinhui et al., 2017). Flame retardants of a similar structure (polybrominated biphenyls (PBBs)) were applied to plastics in many everyday home products in the United States before 1976 (ATSDR, 2004). PBBs exposure is still widespread in the US decades later (Sjödin et al., 2008).

- **Organophosphate Flame Retardants (PFRs)**

The environmentally persistent flame retardants organophosphates have been used since the 1970s in consumer products (Zhang et al., 2016) when countries like the US, Europe, among other countries, restricted using polybrominated diphenyl ethers by manufacturers and decided to use organophosphate flame retardants as a replacement, such as organophosphate tri-esters [tris(2-chloroethyl) phosphate (TCEP), tris(chloropropyl)

phosphate (TCIPP), triphenyl phosphate (TPHP), and tris(1,3-dichloro-2-propyl) phosphate (TDCIPP) (Stapleton et al., 2011; van der Veen & de Boer, 2012).

These chemicals are added to polyurethane foams (mostly found in furniture and car seats and other items) to meet federal and state flammability standards (Stapleton et al., 2012). Firemaster® 550 comprising of [bis(2-ethylhexyl) tetra-bromo-phthalate (BEH-TEBP and 2-ethylhexyl) 2,3,4,5-tetrabromobenzoate (EH-TBB)] is used to replace polybrominated diphenyl ethers along with triphenyl phosphate as well as isopropyl-phenyl diphenyl phosphate (ip-PDPP), indicating that these chemicals are abundant in the indoor environment in most homes (Ali et al., 2012a; Ali et al., 2012b; Bergh et al., 2011; Cequier et al., 2015; Dodson et al., 2012; Schreder et al., 2016). They were detected in > 95% of dust samples in US homes (Stapleton et al., 2009), in many children's products (Bergh et al., 2011; Bradman et al., 2014; Fromme et al., 2014) and also in adults and children urine samples (Hoffman et al., 2014; Hoffman et al., 2015a; Stapleton et al., 2011).

The health risks of exposure to PFRs are causing increasing concern. TPHP exposure has been associated with reproductive and developmental effects, neurotoxicity, genotoxicity, as well as affecting the metabolic and the endocrine system (Du et al., 2016; Krivoshiev et al., 2016; Mendelsohn et al., 2016; Zhang et al., 2014; Zhang et al., 2016). Furthermore, the State of California has classified TCEP and TDCIPP (which are among the most commonly utilized PFRs) as carcinogens (OEHHA, 2011; State of California, 2016).

Phthalates (PAEs)

Phthalates, or phthalic acid esters (PAEs), are plasticizers applied to many of consumer products and building materials (Ma et al., 2014). Consequently, high concentrations of

phthalates can be found in the dust and also in the air in both residential and occupational locations (Abb et al., 2009; Albar et al., 2017; Al Qasmi et al., 2019; Guo & Kannan, 2011; Kang et al., 2012; Kubwabo et al., 2013; Kweon et al., 2018; Langer et al., 2010; Ma et al., 2014; Subedi et al., 2017; Zhang et al., 2013; Zhu et al., 2019). Results published in different studies reveal that PAEs levels in indoor dust are three to five folds higher than PAHs levels (Langer et al., 2010). PAEs are able to disturb human sexual development, as well as the human hormonal and reproduction system (Kay et al., 2013; Kay et al., 2014). Furthermore, they are supposed to cause asthma and skin diseases (Wormuth et al., 2006). In 2005, the European Union listed bis benzyl butyl-phthalate (BBP), dibutyl phthalate (DBP), and bis(2-ethylhexyl) phthalate (DEHP) as harmful substances, and issued a directive prohibiting their use in products, especially cosmetics and toys (Directive 2005/84/EC).

Pesticides

Pesticides have been identified in the indoor environment such as indoor dust (Butte & Heinzow, 2002; Bradman et al., 2006; Colt et al., 2004; Harnly et al., 2009; McCauley et al., 2001; Roberts et al., 2009; Rudel et al., 2003; Simcox et al., 1995). In urban areas, poor housing conditions (like housing disrepair and overcrowding) are linked to infestations of pests and increasing pesticide home usage (Bradman et al., 2005; Whyatt et al., 2002), therefore raising pesticide residues indoors. Moreover, in agricultural areas, the existence of farmworkers in the house, as well as the presence of houses close to the fields have been related to high concentrations of indoor pesticides (Harnly et al., 2009; Lu et al., 2000).

Studies revealed that the persistence of pesticide compounds in indoor dust is owed to the absence of factors that enable their degradation, such as rain, sunlight, microbial action, and high temperature (Roberts et al., 2009).

Pesticides that are semi-volatile or non-volatile have chemical characteristics that enhance particle binding affinity and the capacity to adsorb onto surfaces, dust, and carpet, resulting in expanding their indoor persistence (Butte & Heinzow, 2002). Pyrethroid pesticides, for example, have low vapor pressures and high octanol/water (Kow) and water/organic carbon (Koc) partition coefficients, allowing for easier partition into organic matters and lipids, as well as easier binding to dust particles (Egeghy et al., 2007). As a result, some studies demonstrate that indoor dust is an effective route for pesticides' exposure (Butte & Heinzow, 2002; Curl et al., 2002; Roberts et al., 2009; Simcox et al., 1995). Because of their regular hand-to-mouth movement and continuous touch with surfaces, children are mostly vulnerable to pesticide exposure via contaminated dust ingestion (Roberts et al., 2009).

Pesticides can also exist in indoor dust due to direct applications by applicators and homeowners, as well as the transport of wind, humans, and animals from outside environments (Gunier et al., 2016; Richards et al., 2016). Organochlorine pesticides (OCPs), such as DDT and its degradation products, have extreme developmental and carcinogenic effects (Colborn et al., 1993; Rogan & Ragan, 2007). Even though OCPs are now prohibited, their substitutes, like organophosphorus pesticides, are very neurotoxic and persistent in utero. Postnatal exposures have been linked to altered fetal growth, neurodevelopment, and shorter gestational length in children (Engel et al., 2007; Rauh et al., 2006).

Alkylphenols

Alkylphenols and their ethoxylates (APEs) are commonly used in detergents and cleaning products as surfactants. They are also used in personal, industrial, and agricultural products, paints, pesticides, and oilfields. They are among the most highly concentrated chemicals present in US indoor dust (Mitro et al., 2016) and can be found in food, drinking water, and air (Benotti et al., 2009; Rudel et al., 2010). Consequently, they can be detected in human blood, urine, and breast milk (Calafat et al., 2008).

In wastewater effluent and sediment, APEs have been found in high concentrations (Meador et al., 2016). They degrade into persistent chemicals like nonylphenol and octylphenol, which have up to 60 years of half-life in marine sediments. These chemicals have been found in sediment and surface water samples, and they accumulate in wildlife. Huge quantities are released into the atmosphere simply due to their use in industrial laundry detergents. Over two million pounds are reported to have been released to wastewater treatment plants in California alone. The harmful effects of APEs on fish and wildlife are a significant source of concern regarding their release into the environment (DTSC, 2018). APEs' impacts on human health (including nervous, reproductive, and immune system effects) are also sources of concern (Acir & Guenther, 2018).

3- Biological Contaminants I Indoor Dust

A. Microbiota

Indoor dust microbiota is the primary source for domestic microbial taxa that contains soil and plant particles, in addition to human and animal skin and excretions that accumulate on surfaces. The microbiome in indoor dust can affect human health (according

to its amount and diversity) as dust microbes and their products are suspended or resuspended in the air and make a substantial exposure route via inhalation (Hospodsky et al., 2012, 2015; Macher, 2001).

The sources of fungi in indoor dust may include whole fungal conidia (such as *Helminthosporium* and *Alternaria*), fungal spores (such as *Penicillium* and *Aspergillus*), and different sizes of spore fragments (Rintala et al., 2012). Different kinds of volatile and non-volatile compounds can be found in these fungi and spores, such as (1-3)-β-D-glucan, ergosterol, and mycotoxins. These components have the ability to affect human health (Korpi et al., 1997).

Dead and living bacteria, spores, endospores, and smaller fragments of degraded cells are the most common bacterial components found in the dust (Rintala et al., 2012). especially the dust placed on the high shelves for a long time. These bacterial components include *Bacillus adhaerens*, *Bacillus mesentericus*, *Bacillus panis*, *Bacillus prausnitzii*, and *Bacillus ruminates* (Laubach, 1916).

B. House Dust Mites

House Dust Mites are arachnids that range in length from 300 to 400μm and are related to spiders and ticks. The life cycle of house dust lasts about a month, but it depends on the ideal temperature and humidity (25°C and 75% relative humidity). Under optimum conditions, house dust mites will live for one to three months. House dust mites' weight consists of 75% water, so they need to absorb water from the air vapor to maintain optimum humidity to survive. They feed on organic wastes like animal dander, pollen, skin flakes, bacteria, and molds. The stable environment provided inside homes, such as humidity, carpet, plush toys, and bedding, provided the best conditions to house dust mites to survive

and reproduce. There are thirteen species of House dust mites, but the two most widespread and key sources of allergen are *Dermatophogoides farinae* and *Dermatophadoides pteronyssinus*, both from the *Pyroglyphidae* family (Fox, 2017). These mites produce about 19 different allergens classified according to their molecular weight and biochemical characteristics into four groups (Figure-4). Group 1 and 2 allergens responsible for more than 80% of dust mites' allergic reactions in susceptible persons (Thomas et al., 2004).

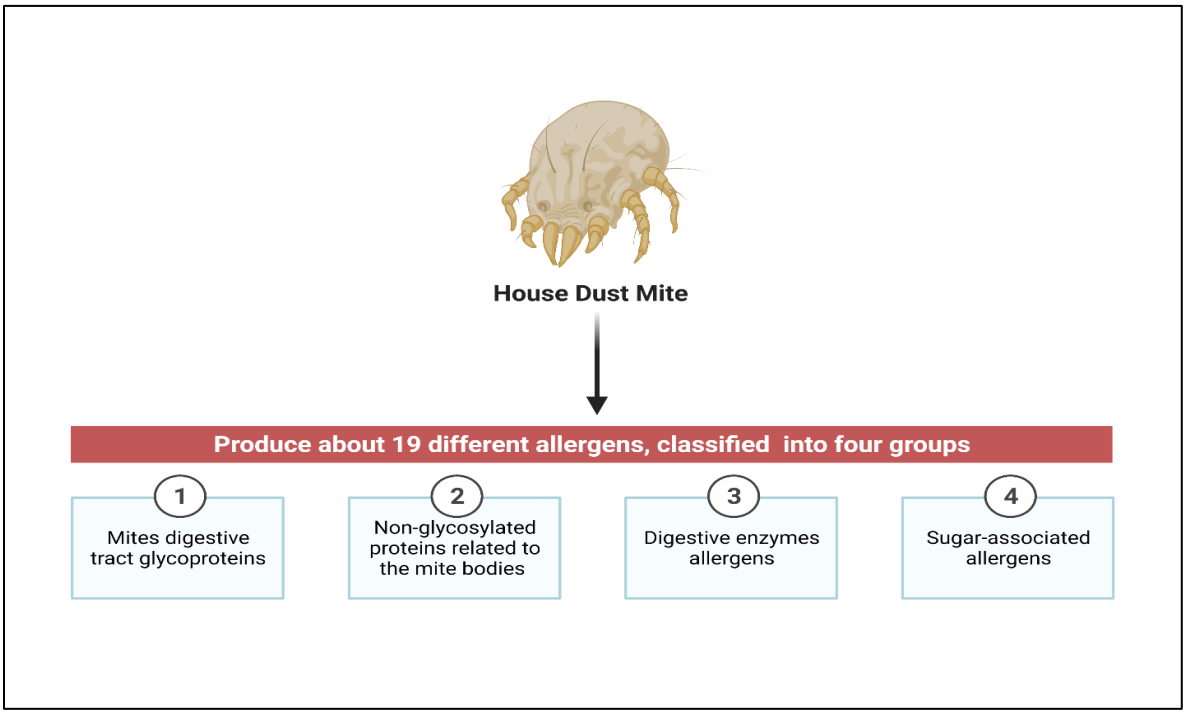


Figure 4: House dust mites' allergens.

House dust mites cause allergies in around 1-2% of the world's population. The hypersensitive immune system reaction to the mite feces results in the house dust mite allergy. Fecal pellets can be easily inhaled when they are air suspended. Sneezing, coughing, wheezing, eye pain, headaches, dizziness, and nausea are all symptoms of an

allergic reaction. In susceptible people, this is a great reason for acute asthma (Colloff, 2009).

House dust mite allergens have proteolytic activities (Holgate, 2008; Page et al., 2010). It has been reported that the serine peptidase activity of these allergens has the ability to cleave junctional proteins, such as E-cadherin (Robinson et al., 1997), and activate the protease-activated receptor (PAR)-2, which participate in the disruption of cell-cell contacts (Winter et al., 2006), and also promote allergic inflammation by facilitating the access of allergens to submucosal cells (Wan et al., 1999; Wan et al., 2001). Moreover, PAR-2 activation by these proteases may induce intracellular signaling pathways activities (such as NF-κB) and promote the secretion of the pro-inflammatory cytokines (such as interleukins) in airway epithelium (Asokananthan et al., 2002; Kauffman et al., 2006).

Several other components of house dust mites may contribute to allergic reactions, such as lipopolysaccharide, chitin/chitinases, and ß-glucan (Elias et al., 2005; Hammad et al., 2009; Nathan et al., 2009).

The Health Risks of Contaminants in Indoor Dust

Outdoor air tends to be the most crucial area of concern to the government in making laws regulating the effects of air pollution on human beings' health conditions. It has also become the target of public concern. However, for the last twenty years, indoor air pollution has emanated in the elevating concern because of the detrimental effects on human health (Tham, 2016).

In the past fifty years, indoor chemicals that are supposed to adversely affect human health have increased due to the establishment of new building materials and consumer

products (Weschler, 2009). These chemicals can leach from products and distribute into indoor air and dust (Ma et al., 2014; Mitro et al., 2016; Rudel et al., 2003).

Significant effects on the respiratory system are attributed to indoor dust exposure, including extreme and chronic pulmonary function changes and sensitization of the respiratory systems to indoor allergens (Pongpiachan, 2016). Lung cancer has been recognized as a crucial disease linked to constant contact with indoor air pollutants.
Several factors influence the nature and probability of indoor dust health impacts; include:

- the size of the particulate matter (smaller particles are considered more harmful),
- the chemical composition of the particulate matter,
- concentration levels of dust,
- duration of exposure,
- other factors, such as age, medical conditions, health status, and genetics.

Many indoor dust chemicals can cause the same health impact, such as reproductive and developmental toxicity or cancer, and can act together. Even small amounts of combined chemicals may lead to increased health risks, particularly for infants or young children. These particles can cause symptomatic effects, such as mucus production, wheeze, and cough (Aditama, 2000; Jinot & Bayard, 1996). At the same time, physiological effects of exposure to these particles can cause acute pulmonary function decrement and bronchial hypersensitivity elevation (Chen et al., 2001; Menon et al., 1992; Morgan et al., 1997; Rudell et al., 1999; Sheppard et al., 1986; Sherman et al., 1989; Wade & Newman 1993). Exposure to dust particles can also cause peripheral blood changes, including increased fibrinogen, blood viscosity, and white blood cell counts (Ghio et al., 2000; Pekkanen et al., 2000; Peters et al., 1997; Pope et al., 1999; Seaton et al., 1999).

Besides, exposure to these particles have been linked to cardiovascular diseases (Dominici et al., 2005; Edling & Axelson, 1984; Krewski et al., 2005; Melius, 1995; Zhu et al., 1993).

Indoor dust contaminants, such as flame retardants and semi-volatile compounds, may turn on peroxisome proliferator-activated nuclear receptor gamma (PPAR-gamma) that involved in obesity by triggering fat cells to grow (Fang et al., 2015).

Bacteria and fungi in household dust can produce their own chemicals that act as allergens and have been linked to skin conditions such as eczema and dermatitis (Nankervis et al., 2015). Figure-5 illustrates most of the health risks associated with exposure to indoor dust.

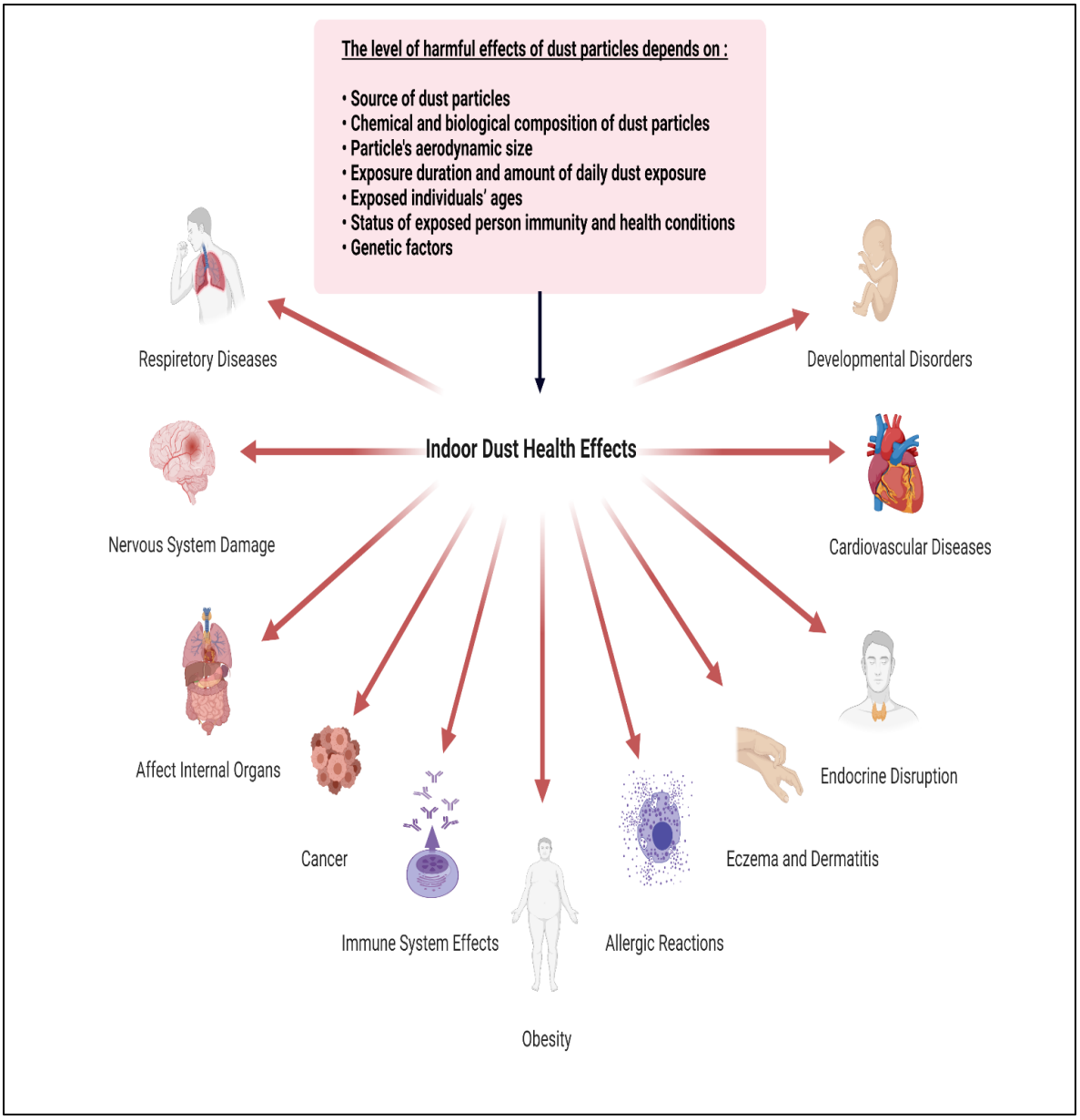


Figure 5: Health risks associated with indoor dust exposure

Cell Death Induced by Particulate Matter

A complex balance between regeneration and cell death is needed for organismal homeostasis. Exposure to particulate matter will interrupt this equilibrium by triggering the key mechanism of cell death. The common agreement is that PM causes the death of cells through inflammatory-associated oxidative stress and DNA damage (Danielsen et al.,

2011; Gasparotto et al., 2013; Jarvela et al., 2013; Longhin et al., 2016; Møller et al., 2014; Sanchez-Perez et al., 2009; Shang et al., 2014; Shrotriya et al., 2015; Thomson et al., 2015). Reports show that PM10 and PM2.5 exposure didn't trigger apparent cell death of the lungs' epithelium (Pavagadhi et al., 2013; Reyes-Zarate et al., 2016; Sanchez-Perez et al., 2014). Alternatively, apoptosis and cell proliferation occurred concurrently (Abbas et al., 2010; Andrysík et al., 2011). PM-triggered pathologic changes, and tumorigenesis were caused by the simultaneous imbalance and activation of the two antagonistic phenomena. Nonetheless, other in vitro and in vivo research have already shown a rise in apoptotic mechanisms of cell death after exposure to PM2.5 (Che et al., 2014; Soberanes et al., 2009; Y Liu et al., 2015), cigarette smoke (Shetty et al., 2012), and cement dust (Ogunbileje et al., 2014). This variation apparently may be owed to the culture variations conditions, the cell lines used, the particle features, and the exposure doses (Turner et al., 2015). Toxicity consequences of particles can induce apoptosis by activating both the extrinsic (caspase-8, -3 activation and tumor necrosis-alpha secretion) and intrinsic (caspase-9, cytochrome-c release, and caspase-3 activation) pathways (Dagher et al., 2006; Deng et al., 2014; Visalli et al., 2015). Particulate matter and their adsorbed chemical species are known for disrupting the formation of DNA and cause DNA breaks and adducts, which can cause cell death (Dagher et al., 2006; Danielsen et al., 2011; Møller et al., 2014, 2008; Nemmar et al., 2013; Perrone et al., 2013; Salcido-Neyoy et al., 2015; Sanchez-Perez et al., 2009; Soberanes et al., 2006).

Usually, necrosis is slightly happened as a result of exposure to particles and particle-associated toxicants (Deng et al., 2014; Oya et al., 2011). Nevertheless, evidence shows that reactive oxygen species (by inhibiting the caspase cascade and activating poly

(ADP-ribose), can cause modification in cell death mode (Wickenden et al., 2003). For example, when high doses are used, the proliferations of human aortic smooth muscle cells are reduced by the wood smoke resulting in necrosis rather than apoptosis (Pan et al., 2013). Furthermore, upregulation of cytokines and exacerbation of reactive oxygen species activity has been involved in a necrotic death of a cell in cases of severe, caspase-independent, and uncontrolled inflammatory response (Bourgeois & Owens, 2014). Despite the fact that the cell death forms are commonly viewed independently, they are all triggered in the same way (Deng et al., 2014). The actual response will be determined by the toxic components in the particles, the period of exposure, and the cellular features.

In fact, the cell death pathway selection is strongly linked with the strength of oxidative stress. As soon as the level of ROS is still tolerable, and the cells still sustain their normal metabolism, they select the apoptotic death pathway to avoid inflammation and damaged-cell proliferation (Guo et al., 2012). However, the increase in ROS can lead to autophagosome formation by oxidized proteins to protect other cells by preventing further oxidative stress (Shrotriya et al., 2015). Furthermore, the intense increase in ROS generation may cause apoptotic protein inhibition and cell autophagy as an alternate pathway (Csordas et al., 2011). Exposure to high concentrations of particulate matter for a short time might lead to so much cellular damage and mitochondrial dysfunction resulting in cell fate shift to necrotic death (Pan et al., 2013).

Reactive Oxygen Species (ROS) and Oxidative Stress

The imbalance between the formation of free radicals and their elimination by defensive mechanisms (such as antioxidants) is defined as oxidative stress (Stefanson &

Bakovic, 2014). This imbalance can affect the entire organism as a result of damage to cells and critical essential cellular biomolecules (Durackova, 2010).

Reactive oxygen species are products of normal cellular metabolism that perform an important role in stimulating signaling pathways in animal and plant cells as a results of variations in environmental conditions (Jabs, 1999). The mitochondrial respiratory chain in cells generates the vast majority of ROS (Poyton et al., 2009). As natural byproducts of biological molecular oxygen reduction, aerobic cells generate free radicals like superoxide anion, hydroxyl radical, hydrogen peroxide, and organic peroxides during endogenous metabolic reactions (Fridovich, 1978). They can oxidize cellular membranes, nucleic acids, proteins, and lipids via uncontrolled reactions if their levels rise above buffering ability. The oxidation and modification of proteins and lipids can increase the chance of mutagenesis (Reuter et al., 2010; Dreger et al., 2009).

Metals found in particulate matter can cause oxidative tissue damage by causing free radicals' formation (Li et al., 2008). Reactive oxygen species may operate as an intracellular or intercellular messenger, activating gene expression and cell signaling cascades (Forman & Torres, 2002; Hancock et al., 2001).

Antioxidant Defense Mechanism

The degree to which primary antioxidant defenses eliminate excessive free radicals can determine the level of oxidative damage control (Kelly, 2003; Weichenthal et al., 2013). Some studies found that exposure to particulate matter can up-regulate the expression and activity of antioxidant enzyme, and trigger the consistent signaling pathways that control intracellular defense mechanisms (Deng et al., 2013; Guerra et al., 2013; Messier et al., 2013; Pardo et al., 2015), while others found that PM exposure down-

regulated antioxidative defense mechanisms (Davel et al., 2012; Delfino et al., 2008; Deng et al., 2013; Guerra et al., 2013; Liu & Meng, 2008; Wang et al., 2015). The variation in these results can be assigned to the variations in several factors, such as PM composition and concentration, the study design, and the host's active defense capacity (Xuemei et al., 2019).

First Line Defense Antioxidants

The antioxidants that counteract or inhibit the production of intracellular reactive species are called the first-line defense antioxidants. They neutralize any molecule with the potential to become a free radical, as well as any free radical with the potential to induce the production of more radicals in a very short amount of time. The top three enzymes are superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). Correspondingly, they can dismutate superoxide radicals, breakdown hydrogen peroxides and hydroperoxides into less harmful molecules (water/alcohol and oxygen). Metal ion binding proteins (such as transferrin and caeruloplasmin) are also included in this class of defense mechanism, which are able to prevent the production of free radical by chelating or sequestering copper and iron (Figure 6) (Ighodaro & Akinloye, 2018).

Superoxide Dismutase (SOD). This enzyme is the first and most powerful endogenous enzyme that acts as the first line of protection against ROS. It has the ability to convert two molecules of superoxide anion into molecular oxygen and hydrogen peroxide, turning the dangerous superoxide anion less harmful (Dringen et al., 2005; Fridovich, 1995).

Catalase (CAT). It is an antioxidant enzyme that can be abundantly found in nearly all living tissues that use oxygen. It is located mainly in the peroxisomes of mammalian

cells but not present in mitochondria. This enzyme is able to catalyze the oxidation or reduction of hydrogen peroxide to molecular oxygen and water (using cofactors, such as iron or manganese) to complete the detoxification step imitated by the SOD enzyme. It is highly effective in breaking down million's molecules of hydrogen peroxide in a single second. (Chelikani & Fita, 2004; Marklund, 1984).

Glutathione Peroxidases (GPx). It is an essential intracellular enzyme that catalyzes the hydrogen peroxides breakdown to water; and lipid peroxides to their resultant alcohols, mostly in the mitochondria and occasionally in the cytosol (Góth et al., 2004). Generally, this enzyme depends on a micronutrient cofactor called selenium to be active. Because of that, glutathione peroxidase is also known as selenocysteine peroxidase. It has a significant role in cell protection from oxidative stress by preventing lipid peroxidation (Gill & Tuteja, 2010).

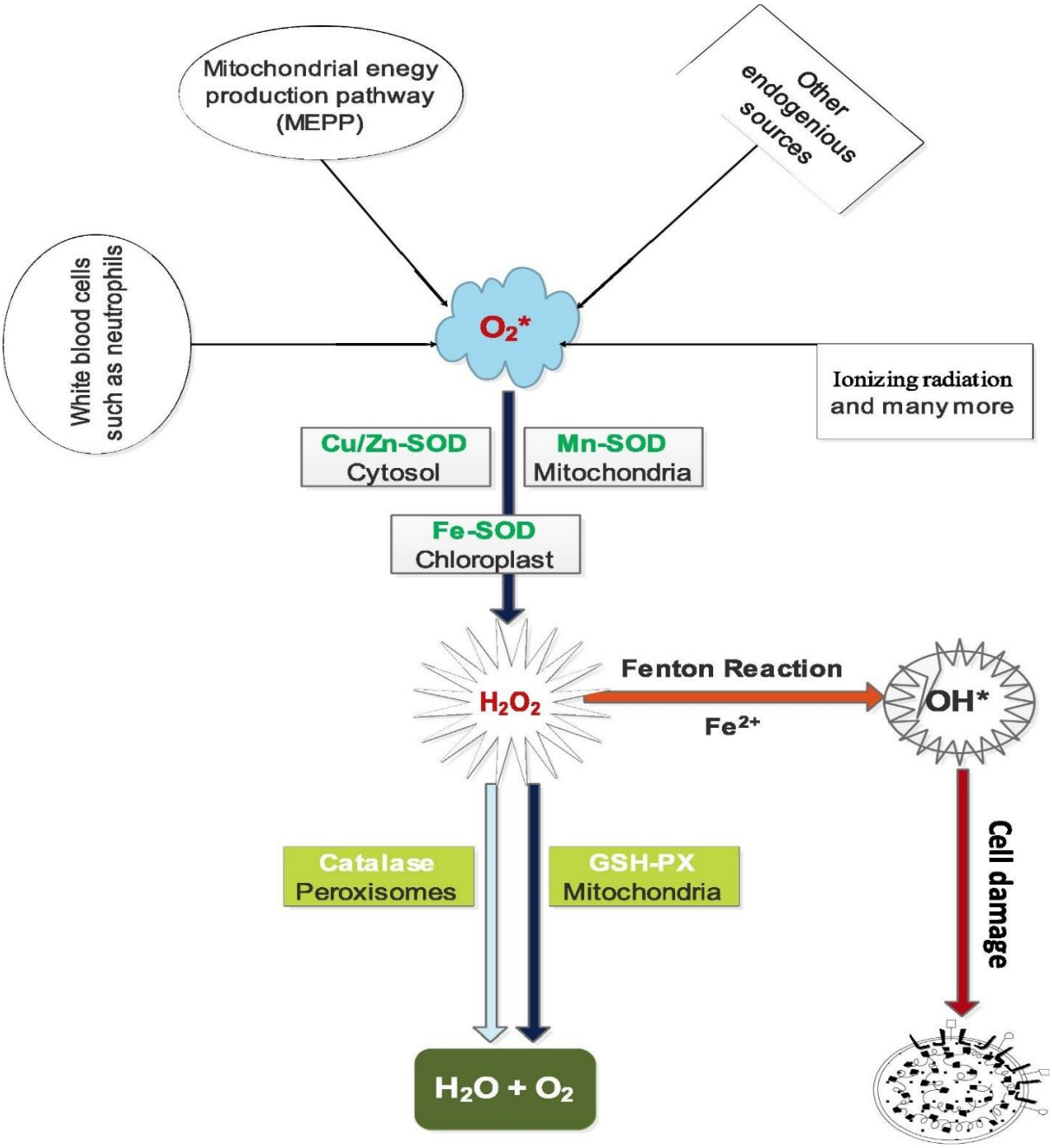


Figure 6: First-line defense antioxidant enzymes. (Ighodaro & Akinloye, 2018).

Inflammation

It is a crucial mechanism for the production of particle-associated health impacts (Donaldson et al., 2001; Kelly & Fussell, 2011; Salvi & Holgate, 1999). There is a clear indication that PM exposure causes the induction or aggravation of airway inflammatory responses, in addition to the induction or aggravation of respiratory diseases (Donaldson & Tran, 2002; Kelly & Fussell, 2011; Kim et al., 2015; Nel et al., 2001; Li et al., 2015, Salvi & Holgate, 1999). Inflammatory reactions are also thought to play a role in producing cancer and fibrosis caused by particles and fibers like asbestos and quartz (Donaldson & Tran, 2002; Manning et al., 2002; Schins, 2002). Pulmonary inflammation is also considered to be an important cause of cardiovascular diseases after exposure to particles because it can trigger the release of cytokines and other pro-inflammatory or pro-thrombotic compounds into the bloodstream, causing arterial remodeling (Donaldson et al., 2001; Grunig et al., 2014; Schulz et al., 2005; Terzano et al., 2010). As a result, one of the most critical aspects of particle toxicology is finding out how the particles cause an inflammatory response in the airway.

Lung inflammation is caused by a more than one type of cells, including epithelial cells lining the airways and alveoli, and immune cells in the bloodstream. Airway epithelial cells play a significant role in the defense mechanism by functioning as a physical barrier, and by catching the inhaled particles via their mucus secretions (Adler & Li, 2001). They can also secrete antimicrobial proteases that counteract the hazard (Aarbiou et al., 2002; Kota et al., 2008; McCray & Bentley, 1997), inflammatory mediators, such as cytokines and chemokines (Hellermann et al., 2002; Herfs et al., 2012; Mills et al., 1999; Takizawa et al., 2000), and growth factors that promote tissue repair (Takizawa et al., 2001). Some

research has revealed that the alveolar epithelial cells and mesothelial cells in body cavities can activate the inflammatory response in the absence of immune cells through the NLRP3 inflammasome after exposure to pathogenic particles (Sayan & Mossman, 2016).

NLRP3 Inflammasome

NLRP3 is a group of cytosolic protein complexes that control inflammation, releasing certain proinflammatory cytokines, which stimulate the host's immune response. When environmental particles or nanoparticles stimulate cells, the inflammasome is required to maitain an equilibrium between pro-inflammatory and anti-inflammatory signals in order to produce an effective immune response without damaging the host (Abais et al., 2015) by recruiting the apoptosis-associated speck protein (ASC) (Baroja-Mazo et al., 2014). The inflammasome can activate pro-caspase-1 (a cysteine protease that introduces or executes cellular programs, leading to inflammation or cell death). Active caspase-1 cleaves a key proinflammatory cytokine (pro-IL-1) into its active form to regulate the severity of inflammation in a variety of diseases (Martinon et al., 2002).

Studies indicated that inhaled pathogenic fibers and particles could prime and activate inflammasomes in both acute and chronic inflammation. Acute inflammation after exposure to low doses of particles can be protective against inhaled toxins by triggering repair responses, while chronic inflammation is seen at high doses of particles and fibers (Sayan & Mossman, 2016).

Caspase-1 and Cell Death

The activation of caspase-1 commonly leads to inflammation, while excessive activity leads to pyroptosis. Pyroptosis is a non-apoptotic cell-programmed death marked by a rupture in plasma membranes, and the release of pro-inflammatory mediators

(Cookson & Brennan, 2001; Fink & Cookson, 2006). Active caspase-1 can stimulate caspase-7 and an unspecified nuclease, which cause DNA cleavage and nuclear condensation without affecting the integrity of the nucleus (Bergsbaken & Cookson, 2007; Molofsky et al., 2006). Because caspases-1 activation is necessary for cell death in the immune system, the central nervous system, and the cardiovascular system, Pyrolysis is thought to have a valuable role in human health (Frantz et al., 2003; Kolodgie et al., 2000; Liu et al., 1999; Shi et al., 1996; Yang et al., 1999; Zhang et al., 2003).

Mitogen-Activated Protein Kinases (MAPK)

Mitogen-activated protein kinases are the major signaling pathways that control a broad diversity of cellular activities, such as stress responses, proliferation, differentiation, and programmed cell death in both pathological and normal states (Guo et al., 2020).

MAPKs are ubiquitous serine-threonine kinases that are evolutionarily conserved and are part of a central pathway that includes MAPK-kinase-kinase (MAPKKK), MAPK-Kinase (MAPKK), and MAPK (Figure 7). MAPKKK can be activated by different stimuli, such as mitogens and growth factors, to phosphorylate MAPKK. The activated MAPKK then phosphorylates MAPK (Munshi & Ramesh, 2013). C-Jun N-terminal kinase/stress-activated protein kinase (JNK/SAPK), extracellular signal-regulated kinase (ERK), and p38 kinase are the three MAPK families that have been identified in mammalian cells (Zhang & Liu, 2020).

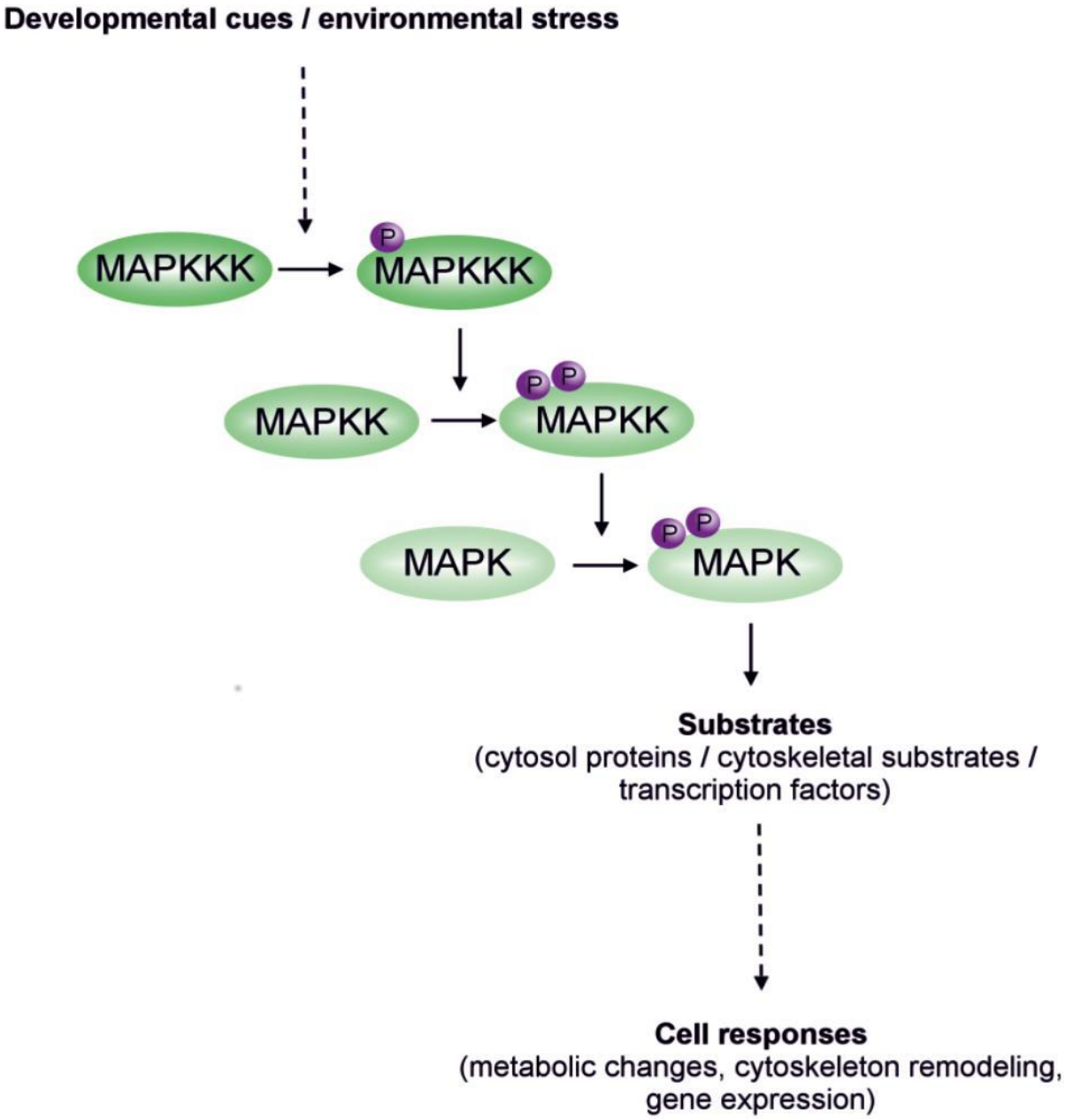


Figure 7: Schematic description of MAPK cascade (Jagodzik et al., 2018).

The JNK Kinase Family

It consists of three types, which are JNK1, JNK2, and JNK3. All tissues contain the JNK1 and JNK2, while JNK3 is found only in the testes, the brain, and the heart. Many factors can activate JNK, such as pathogens, cytokines, stress, growth factors, among others. Abnormalities in JNK activity are linked to neurodegenerative disorders, cancer, inflammatory disorders, and diabetes. (Bubici et al., 2014; Fey et al., 2012; Zhang et al., 2002).

The ERK Kinase Family

The ERK kinase family includes ERK1 and ERK2. A variety of mitogens and growth factors participate in the activation of this family. MEK phosphorylation is the first step in ERK activation, followed by the threonine and tyrosine residues phosphorylation. Activated ERK can phosphorylate other proteins (responsible for cell division, growth, regulation, and differentiation) after moving to the cytoplasm and nucleus. (Fey et al., 2012; Seger et al., 1995; Zhang et al., 2002).

The p38 Kinase

Many extracellular stimuli can activate p38 kinase, such as growth factors, inflammatory cytokines, lipopolysaccharides, UV radiation, and osmotic shock. Several kinases are also involved in p38 activation, including MKK3, MKK6, MKK4. The activation of p38 is associated with several disease conditions, such as autoimmunity, asthma, and inflammation (Johnson et al., 2002).

CHAPTER 3

DESIGN OF THE STUDY

Reagents

Keratinocyte-serum free medium (K-SFM), Phosphate-Buffered saline (PBS), and Antibiotic-Antimycotic (Anti-Anti) were purchased from Gibco by Life Technologies. Dimethyl Sulfoxide (DMSO) was purchased from Thermo Fisher Scientific (USA). Tris Buffered Saline (TBS), Tris/Glysin/SDS (TGS), and Tween-20 were purchased from Bio-Rad Laboratories (USA).

Indoor Dust Samples

Two types of indoor dust were used in this experiment, which were supplied by the National Institute of Standards and Technology (NIST, Gaithersburg, MD, USA):

Standard Reference Material 2584: Trace Elements in Indoor Dust (1% Lead):

The toxic trace elements As, Cd, Cr, Pb, and Hg have been certified in this SRM

Table 1: Certified and reference mass fractions for trace metals in SRM 2584

Certified Trace Metals	Mass Fraction (µg/kg)
Arsenic (As)	17.4 ± 4.2
Cadmium (Cd)	10.0 ± 1.1
Chromium (Cr)	135.0 ± 9.1
Lead (Pb)	9761 ± 67
Mercury (Hg)	5.20 ± 0.24

Reference Trace Metals	
Aluminum (Al)	23 200 ± 600
Calcium (Ca)	63 300 ± 3 000
Iron (Fe)	16 400 ± 1 200
Potassium (K)	9 500 ± 1 400
Lanthanum (La)	19 ± 2
Magnesium (Mg)	15 900 ± 300
Sodium (Na)	27 700 ± 1 200
Phosphorus (P)	2 000 ± 120
Titanium (Ti)	4 200 ± 300
Zinc (Zn)	2 580 ± 150

Standard Reference Material 2585: Organic Contaminants in House Dust:

This complex reference material contains trace amounts of PAHs, PCB congeners, chlorinated pesticides, and PBDE congeners.

Table 2: Certified mass fractions for selected PAHs, PCB Congeners, Chlorinated Pesticides, and PBDE Congeners in SRM 2585

PAHs	Mass Fraction (µg/kg)
1-Methylphenanthrene	197 ± 29
2-Methylphenathrene	352 ± 40
3-Methylphenanthrene	293 ± 36
4H-cyclopenta[def]phenanthrene	117 ± 10

9-Methylphenanthrene	205 ± 16
Anthracene	96.0 ± 5.2
Benz[a]anthracene	1160 ± 54
Benzo[a]fluoranthene	74.5 ± 8.1
Benzo[a]pyrene	1140 ± 10
Benzo[b]chrysene	182 ± 6
Benzo[b]fluoranthene	2700 ± 90
Benzo[c]phenanthrene	288 ± 10
Benzo[e]pyrene	2160 ± 80
Benzo[ghi]fluoranthene	3290 ± 30
Benzo[ghi]perylene	2280 ± 40
Benzo[j]fluoranthene	1320 ± 110
Benzo[k]fluoranthene	1330 ± 70
Chrysene	2260 ± 60
Coronene	603 ± 38
Dibenz[a,c]anthracene	183 ± 25
Dibenz[a,h]anthracene	301 ± 50
Dibenz[a,j]anthracene	267 ± 9
Dibenzo[a,e]pyrene	477 ± 67
Dibenzo[b,k]fluoranthene	596 ± 22
Dibenzothiophene	109 ± 8
Fluoranthene	4380 ± 100
Indeno[1,2,3-cd]pyrene	2080 ± 100
Naphthalene	266 ± 8
Perylene	387 ± 23
Phenanthrene	1920 ± 20
Picene	413 ± 15
Pyrene	3290 ± 30

Triphenylene	589 ± 17
PCB Congeners	
PCB 18 (2,2',5-Trichlorobiphenyl)	12.8 ± 1.0
PCB 28 (2,4,4'-Trichlorobiphenyl)	13.4 ± 0.5
PCB 31 (2,4',5-Trichlorobiphenyl)	14.0 ± 0.5
PCB 44 (2,2'3,5'-Tetrachlorobiphenyl)	18.1 ± 1.9
PCB 52 (2,2',5,5'-Tetrachlorobiphenyl)	21.8 ± 1.9
PCB 56 (2,3,3',4-Tetrachlorobiphenyl)	4.42 ± 0.28
PCB 70 (2,3',4',5-Tetrachlorobiphenyl)	13.1 ± 1.2
PCB 74 (2,4,4',5-Tetrachlorobiphenyl)	5.22 ± 0.51
PCB 87 (2,2',3,4,5'-Pentachlorobiphenyl)	16.6 ± 0.8
PCB 92 (2,2',3,5,5'-Pentachlorobiphenyl)	5.48 ± 0.72
PCB 95 (2,2',3,5',6-Pentachlorobiphenyl)	22.7 ± 2.6
PCB 99 (2,2',4,4',5-Pentachlorobiphenyl)	11.6 ± 0.4
PCB 101 (2,2',4,5,5'-Pentachlorobiphenyl)	29.8 ± 2.3
PCB 105 (2,3,3',4,4'-Pentachlorobiphenyl)	13.2 ± 1.4
PCB 107 (2,3,3',4,5'-Pentachlorobiphenyl)	4.14 ± 0.47
PCB 110 (2,3,3',4',6-Pentachlorobiphenyl)	28.1 ± 3.7
PCB 118 (2,3',4,4',5-Pentachlorobiphenyl)	26.3 ± 1.7
PCB 132 (2,2',3,3',4,6'-Hexachlorobiphenyl)	40.2 ± 1.8
PCB 138 (2,2',3,4,4',5'-Hexachlorobiphenyl)	27.6 ± 2.1
PCB 146 (2,2',3,4',5,5'-Hexachlorobiphenyl)	4.89 ± 0.38
PCB 149 (2,2',3,4',5',6-Hexachlorobiphenyl)	24.4 ± 1.9
PCB 151 (2,2',3,5,5',6-Hexachlorobiphenyl)	6.92 ± 0.64
PCB 153 (2,2',4,4',5,5'-Hexachlorobiphenyl)	40.2 ± 1.8
PCB 158 (2,3,3',4,4',6-Hexachlorobiphenyl)	4.50 ± 0.43
PCB 163 (2,3,3',4',5,6-Hexachlorobiphenyl)	7.2 ± 1.2
PCB 170 (2,2',3,3',4,4',5-Heptachlorobiphenyl)	8.8 ± 1.0

PCB 174 (2,2',3,3',4,5,6'-Heptachlorobiphenyl)	8.83 ± 0.47
PCB 180 (2,2',3,4,4',5,5'-Heptachlorobiphenyl)	18.4 ± 3.2
PCB 183 (2,2',3,4,4',5',6-Heptachlorobiphenyl)	5.27 ± 0.39
PCB 187 (2,2',3,4',5,5',6-Heptachlorobiphenyl)	11.3 ± 1.4
PCB 206 (2,2',3,3',4,4',5,5',6-Nonachlorobiphenyl)	3.81 ± 0.13
Chlorinated Pesticides	
4,4'-DDE	261 ± 2
4,4'-DDD	27.3 ± 0.8
2,4'-DDT	44.5 ± 3.9
4,4'-DDT	111 ± 23
PBDE Congeners	
PBDE 17 (2,2',4-Tribromodiphenyl Ether)	11.5 ± 1.2
PBDE 28 (2,4,4'-Tribromodiphenyl Ether)	46.9 ± 4.4
PBDE 33 (2',3,4-Tribromodiphenyl Ether)	46.9 ± 4.4
PBDE 47 (2,2',4,4'-Tetrabromodiphenyl Ether)	497 ± 46
PBDE 49 (2,2',4,5'-Tetrabromodiphenyl Ether)	53.5 ± 4.2
PBDE 85 (2,2',3,4,4'-Pentabromodiphenyl Ether)	43.8 ± 1.6
PBDE 99 (2,2',4,4',5-Pentabromodiphenyl Ether)	892 ± 53
PBDE 100 (2,2',4,4',6-Pentabromodiphenyl Ether)	145 ± 11
PBDE 138 (2,2',3,4,4',5'-Hexabromodiphenyl Ether)	15.2 ± 2.0
PBDE 153 (2,2',4,4',5,5'-Hexabromodiphenyl Ether)	119 ± 1
PBDE 154 (2,2',4,4',5,6'-Hexabromodiphenyl Ether)	83.5 ± 2.0
PBDE 155 (2,2',4,4',6,6'-Hexabromodiphenyl Ether)	3.94 ± 0.34
PBDE 183 (2,2',3,4,4',5',6-Heptabromodiphenyl Ether)	43.0 ± 3.5
PBDE 203 (2,2',3,4,4',5,6',6-Octabromodiphenyl Ether)	36.7 ± 6.4
PBDE 206 (2,2',3,3',4,4',5,5',6-Nonabromodiphenyl Ether)	271 ± 42
PBDE 209 (Decabromodiphenyl Ether)	2510 ± 190

Preparation of Dust Samples

Stock solutions of 50 mg/ml for both indoor dust types were prepared in phosphate-buffered saline, vigorously vortexed, stored at -80°C, then diluted with complete media to the final concentrations required on the day of use.

Cell culture

BEAS-2B cells (ATCC® CRL-9609™) are transformed variants of primary cultures of normal human bronchial epithelial cells. These cells were cultured in defined keratinocyte-serum free media (Invitrogen, Carlsbad, CA) supplemented with 5% Bovine Pituitary Extract (BPE), 0.5% EGF, and 1% antibiotic-antimycotic (Invitrogen) and maintained in a humid incubator with 5% CO_2 at 37°C.

Observation of Cell Morphology

After treatment with different indoor dust concentrations (10, 25, 50, 75, 100, 250, and 500 µg/ml) for 24 hours, BEAS-2B cells morphology was observed using an inverted light microscope and compared with the untreated cells. For each treatment, a well of living cells was imaged, and the process was repeated two times using two separate plates.

Cell Viability Assays

The effects of indoor dust on BEAS-2B cells' viability were evaluated using two methods: the MTT assay and the Protease Viability Assay (GF-AFC viability assay).

MTT Assay: This assay was used to evaluate the effect of indoor dust on cell viability depending on the reduction of MTT (3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyl tetrazolium bromide (Sigma-Aldrich) to formazan. BEAS-2B cells (5000 cell/well) were plated in 96-well culture plates and allowed to attach overnight in defined keratinocyte-serum free media (200 µl), after which the media was removed the cells treated with

different concentrations of indoor dust (10, 25, 50, 75, 100, 250, and 500 µg /ml) for 24 hours. The same concentrations of dust were used without cells in each plate as sample controls. Cells exposed to complete media were used as negative controls. 5mg/ml filter-sterilized MTT stock solution was added to each well (20 µl/200 µl media). After 4 hours incubation at 37℃, the supernatant was discarded, and the formed formazan crystals were dissolved at room temperature in 200µl DMSO in each well for 15 minutes. The absorbance measurement was done using a microplate reader at 570 nm. The assay was carried out with three replicates for each culture using three different passages. Cell viability was calculated as the percentage of untreated cells (100%) by normalizing the absorbance to the corresponding control.

Protease Viability Assays (GF-AFC Assay): As a compliment to the results of MTT, the cell protease activity was performed using fluorogenic, cell-permeant peptide substrate (Glycylphenylalanyl-Aminofluorocoumarina (GF-AFC)), which is a part of the triplex assay (ApoTox-Glo Triplex Assay, Promega). This substrate enters only intact cells and cleaved to produce a fluorescent signal equivalent to the living cells number. Five thousand cells/well were seeded in a white 96-well plate overnight, after which the media was removed and the cells treated with solutions of media containing increasing concentrations of dust (10, 25, 50, 75, 100, 250, and 500 µg/ml) for 24 hours. The same concentrations of dust were used without cells in each plate as sample controls. Cells exposed to complete media were used as a negative control. The GF-AFC reagent was added to each well in the plate. After shaking, the plate was incubated for 1 hour at 37°C. Fluorescent signals were measured using a microplate reader at 400Ex/505Em to estimate the viable cell number. The experiment was run in triplicate.

Cell Cytotoxicity Assay (Lactate Dehydrogenase Release)

To quantify the lactate dehydrogenase release into the culture medium after plasma membrane damage, LDH-Glo™ Cytotoxicity Assay kit (Promega) was used. This assay is a sensitive bioluminescent assay allowing precise detection of LDH from a small number of cells in cell cultures. Five thousand cells/well were seeded in each well in a white 96-well plate overnight, then the media was replaced with solutions of media containing increasing concentrations of dust (10, 25, 50, 75, 100, 250, and 500 µg /ml). The same concentrations of dust were used without cells in each plate as sample controls. Cells exposed to complete media were used as a negative control. After incubation with dust samples for 24 hours, 2µl of cell-free supernatants were collected in LDH storage buffer (1:25 dilution), then 50µl of the diluted samples combined with 50µl LDH Detection Reagent. After 60 minutes incubation at room temperature, luminescence was recorded by a microplate reader. The experiment was run in triplicate.

Apoptosis Assay (Caspase-Glo 3/7 Activation)

To detect alveolar cell death in the presence of indoor dust, caspase-3 and 7 (apoptotic markers) activity was measured in BEAS-2B cells using Caspase-Glo® 3/7 assay according to the manufacturer's instructions (ApoTox-Glo Triplex Assay, Promega). The assay does this by lysing the cell and causes the cleavage of the luminogenic caspase 3/7 substrate by caspases to generate a luminescent signal corresponding to the degree of present caspase activity. Five thousand cell/well were seeded in a white 96-well plate overnight, after which the media was removed and the cells treated with solutions of media containing increasing concentrations of dust (10, 25, 50, 75, 100, 250, and 500 µg /ml) for 24 hours. The same concentrations of dust were used without cells in each plate as sample

controls. Cells exposed to complete media were used as a negative control. Then, Caspase-Glo reagent was added to each well with vigorous shaking to lyse cells. After 1 hour incubation at room temperature, luminescence was measured using a microplate reader to detect apoptosis. The experiment was run in triplicate.

Reactive Oxygen Species Detection

To detect the level of ROS in BEAS-2B cells after indoor dust exposure, intracellular and extracellular detection methods were used:

Intracellular Reactive Oxygen Species Detection (H_2DCFDA Assay): After dust exposure, 2′,7′-dichlorofluorescein diacetate (H_2DCFDA) from Invitrogen (Carlsbad, CA, USA) was used to estimate changes in intracellular ROS level. This probe is penetrated into the cytoplasm and hydrolyzed into non-fluorescent DCFH that in the presence of ROS is transformed to a high fluorescent molecule (dichlorofluorescein).

Briefly, BEAS-2B cells were cultured in a 24-well plate and allowed to attach overnight. Then, the media was removed and replaced with 50 and 100 μg/ml of indoor dust. Cells exposed to complete media were used as a negative control. After incubation for 24 hours at 37°C, the cell culture medium was removed and cells washed by PBS. H_2DCFDA was added to each well for 30 min in the dark. Afterward, the cells were visualized by the inverted fluorescent microscope.

Extracellular Reactive Oxygen Species Detection (ROS-Glo™ H_2O_2 Assay): The ROS-Glo H_2O_2 assay is a bioluminescent test that measures the level of hydrogen peroxide (H_2O_2) in a cell culture medium in a fast and sensitive way. It allows the identification of compounds that modify ROS levels.

BEAS-2B cells (5000 cells/well) were plated in 96-well plates and allowed to attach overnight at 37°C. Then, the media was replaced with 50 and 100 µg /ml of indoor dust samples in a total volume of 80 µl/well. The same concentrations of dust were used without cells in each plate as sample controls. Cells exposed to complete media were used as a negative control. After 22 hours of incubation, 20 µl of the H_2O_2 substrate solution was added to each well, and the time was completed to 24 hours in the incubator. Then, 50 µl from each well was mixed with 50 µl of the ROS-Glo detection solution in a white 96-well plate. After incubation for 20 min at room temperature, luminescence measurement (which reflects H_2O_2 level) was done using a microplate reader. Experiments were carried out in triplicate.

Caspase 1-Inflammasome Activity Assay

Bioluminescent Caspase-Glo 1 inflammasome assay (Promega) was used to determine the inflammasome formation in BEAS-2B cells subjected to indoor dust. BEAS-2B cells were seeded at 5000 cell/well in 96-well white-walled plates overnight, after which the media was removed and the cells treated with solutions of media containing increasing concentrations of dust (10, 25, 50, 75, 100, 250, and 500 µg/ml) for 24 hours. The same concentrations of dust were used without cells in each plate as sample controls. Cells exposed to complete media were used as a negative control. Caspase-Glo 1 reagent in an amount of 100µl (with MG132 inhibitor 60 µmol/l final concentration), or Caspase-Glo 1 YVAD-CHO reagent (with Ac-YVAD-CHO inhibitor 1 µmol/l final concentration) were added to each well containing 100 µl of blank, untreated cells, dust-treated cells, and sample controls in the 96-well plate. Using a plate shaker, the plate contents were mixed at a speed of 300 rpm for 30 seconds and then incubated at room temperature for 1 hour.

The luminescence was recorded using a microplate reader. Experiments were carried out in triplicate.

Protein Extraction

Whole-Cell lysates were prepared from BEAS-2B cells exposed to 100 μg/ml for 6, 12, 24, and 48 hours. After exposure, the cells were dissolved in radioimmunoprecipitation assay (RIPA) lysis buffer (25 mM Tris, 150 mM Sodium Chloride, 1% NP-40, 1% Sodium Deoxycholate, 0.1% SDS, pH 7.6) containing 10% protease inhibitor cocktail and 10% phosphatase inhibitor cocktail (Thermo Fisher Scientific, USA) for 30 mins on ice before being centrifuged at 14000xg for 15 minutes. The supernatants were collected and stored at -80˚C., and protein concentration was measured using Pierce™ BCA Protein Assay Kit (Thermo Fisher Scientific, USA).

Antibodies

In western blot analysis, the primary antibodies used were rabbit anti-JNK, rabbit anti–phospho-JNK, rabbit anti-ERK, rabbit anti–phospho-ERK, rabbit anti–p38, rabbit anti–phospho–p38, rabbit anti-SOD1, rabbit anti-SOD2, rabbit anti-CAT, rabbit anti-GPx, rabbit anti-β-actin antibodies (Cell Signaling Technology, Boston, MA). The secondary goat anti-mouse or goat anti-rabbit antibodies used were IRDye 680rd or 800cw labeled (LiCor, Lincoln, NE).

Western Blotting

To measure protein expression, 30μg of protein was loaded in a 10% SDS-PAGE (sodium dodecyl sulfate-polyacrylamide gel electrophoresis) gel and electrically transferred using transfer buffer (25mM Tris, 192mM glycine, 20% methanol, pH8.3) onto a nitrocellulose membrane in the Bio-Rad trans-blot turbo transfer system. Membranes were blocked at room temperature for 1 hour in 5% non-fat dry milk in Tris-

buffered saline solution (TBS). After blocking, primary antibodies of interest were diluted 1:1000 in the blocking buffer and added to membranes overnight at 4°C. After subsequent washing of membranes (three times, 5 min each) by TBS buffer with 0.1% Tween-20, goat anti-mouse or goat anti-rabbit IRDye 680rd or 800cw labeled secondary antibodies diluted 1:10,000 in TBST buffer were added to the membranes and incubated for 1 hour at room temperature. Following secondary labeling, membranes were washed with TBST three times for 5 min each, followed by washing with TBS buffer for 5 min., then imaged to detect bands by LiCor Odyssey imaging system (LiCor, Lincoln, NE).

Statistical Analysis

All data were collected from three independent experiments. For multiple comparisons, a two-way analysis of variance was used. Data were statistically analyzed using GraphPad PRISM software version 8.4. and expressed as mean ± S.D. of triplicates. Differences were considered significant with a probability value of <0.05 (*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$; ****, $p < 0.0001$).

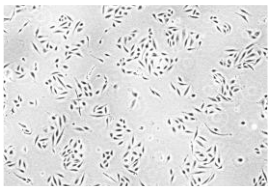
CHAPTER 4

RESULTS AND DISCUSSION

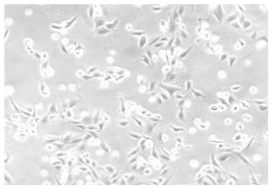
Observation of Cell Morphology

As an important indicator of cytotoxicity, a phase-contrast inverted microscope was used to study the cell morphology after dust exposure (Figure 8). BEAS-2B cell line was treated with different concentrations of both types of indoor dust (10, 25, 50, 75, 100, 250, and 500 µg/ml). After 24 hours, the treated cells were checked and compared with control cells. Most of the cells appear separated from one another neatly with a spindle-like shape, while treated cells appear with clearly atypical shapes with rounding and detaching. Cell density was decreased with increasing dust concentration.

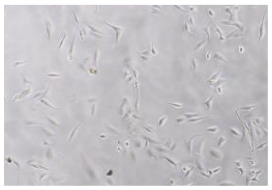
Trace Element Indoor Dust



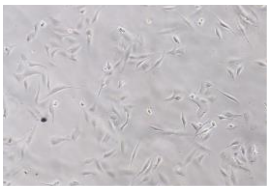
0 µg/ml



10 µg/ml

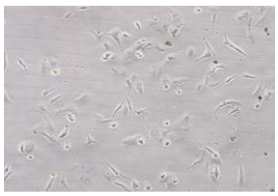


25 µg/ml

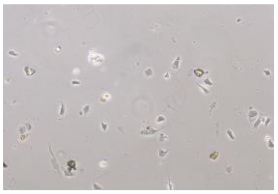


50 µg/ml

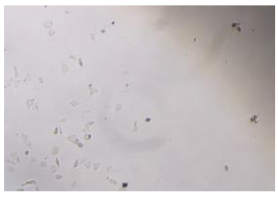
75 µg/ml



100 µg/ml



250 µg/ml



500 µg/ml

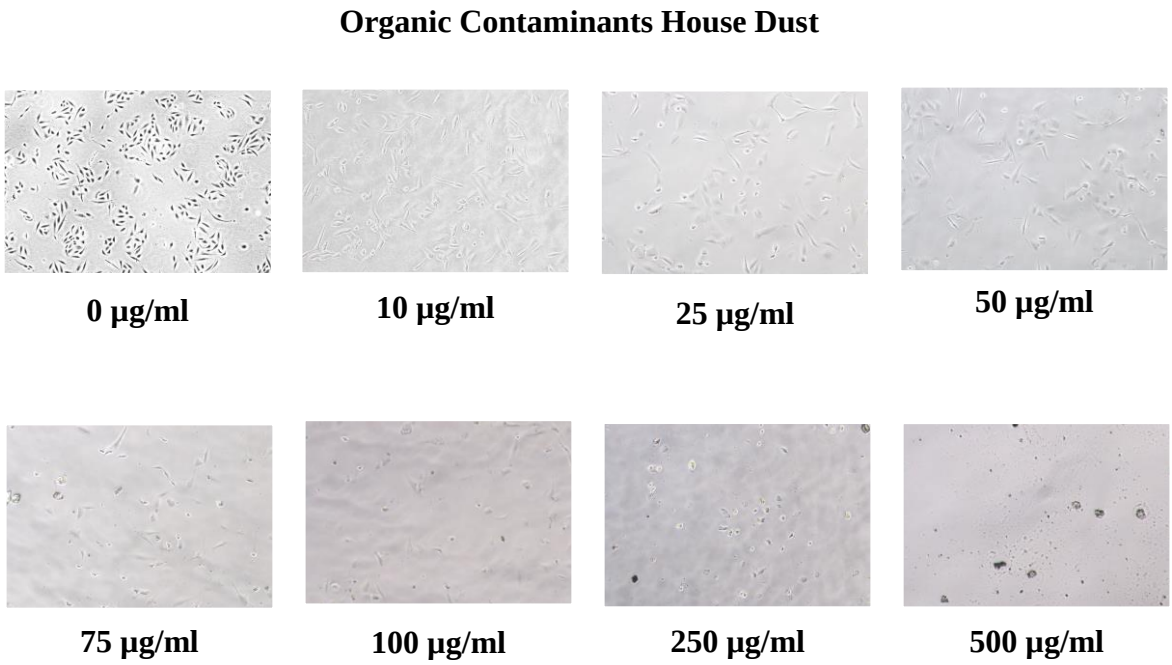


Figure 8: Cellular morphology changes of BEAS-2B cells following 24 hour exposure to different concentrations of Trace Element Indoor Dust and Organic Contaminants in House Dust.

Indoor Dust Exposure Reduces Cell Viability (Metabolic Activity)

Cell viability is a significant predictor of cellular responses to contaminants (Adan et al., 2016). Normal human lung epithelial cells were treated with two indoor dust types classified according to their chemical compositions. Twenty-four hours after exposure to dust at concentrations of 10, 25, 50, 75, 100, 250, and 500 µg/ml, cell viability was assessed by MTT assay and GF-AFC analysis.

As shown in Figure 9 (A and B), both dust samples (Trace Elements dust and Organic contaminants dust) significantly affect the cell viability in a concentration-dependent manner ($p<0.5$). At a higher concentration (500 µg/ml), the cell viability was reduced by up to 85.5% and 91.5% for the Trace Elements dust and Organic contaminants dust, respectively.

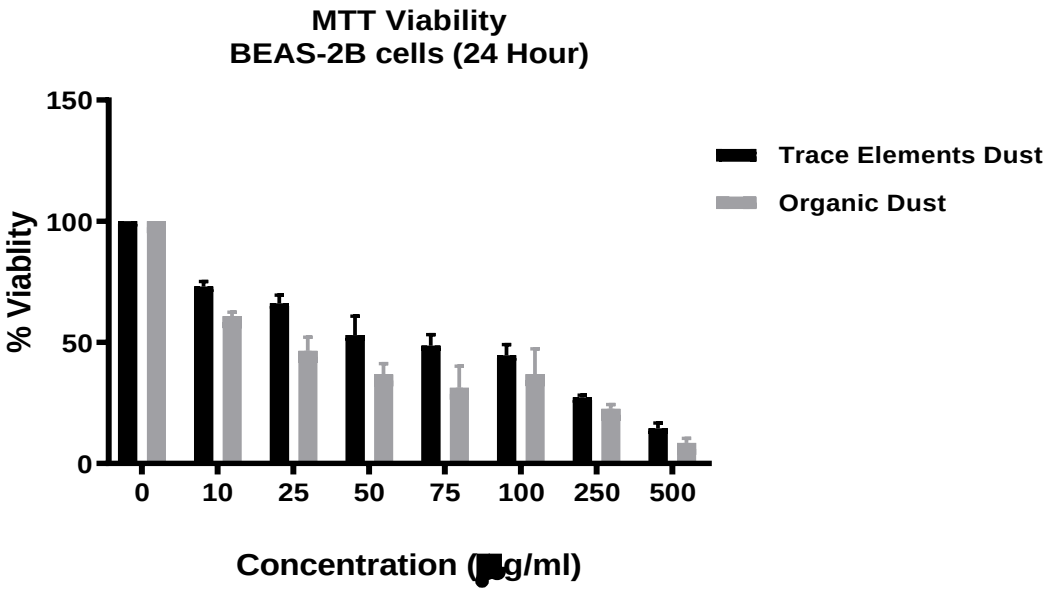


Figure 9 (A): Cell viability (metabolic activity) of normal human lung epithelial cells after exposure to Trace Element Indoor Dust and Organic Contaminants in House Dust (0, 10, 25, 50, 75, 100, 250, and 500 µg/ml) for 24h. The data are expressed as cell viability percentage of the mean + SD of three experiments.

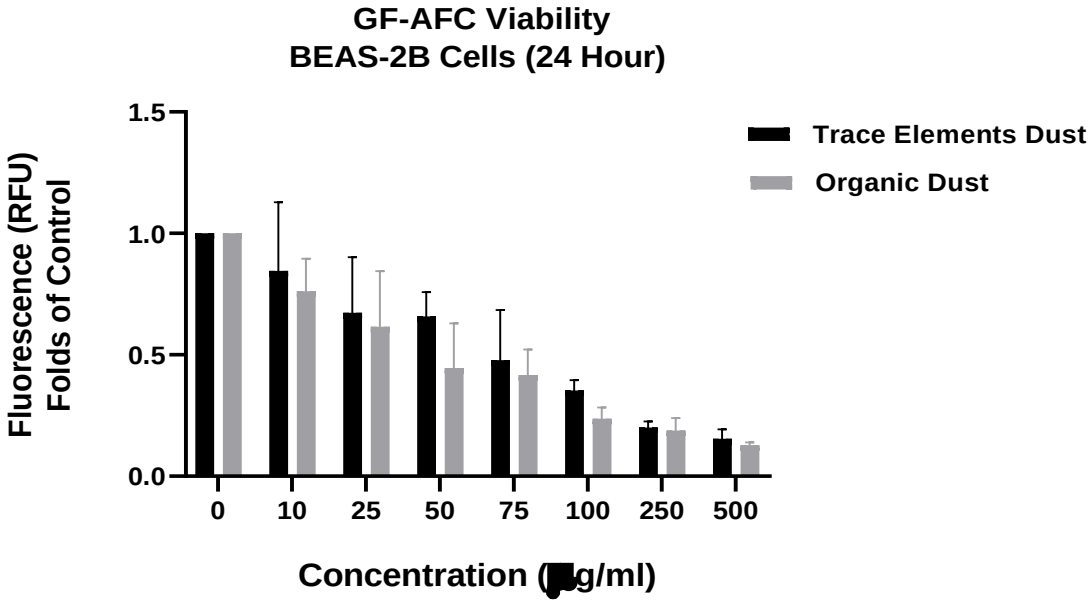


Figure 9 (B): Cell viability (GF-AFC) of normal human lung epithelial cells after exposure to Trace Element Indoor Dust and Organic Contaminants in House Dust (0, 10, 25, 50, 75, 100, 250, and 500 µg/ml) for 24h. The data are expressed as mean + SD fold change of control of three experiments.

Studying cell viability considered a substantial indicator of cellular responses to pollutants (Adan et al., 2016). It was evaluated by two analysis methods, MTT assay and Protease analysis (GF-AFC), after exposure of BEAS-2B cells to different concentrations of indoor dust for 24 hours. Our results show that both types of indoor dust caused a concentration-dependent decrease in lung cell viability.

Indoor Dust Exposure Induces Cell Cytotoxicity (LDH Release)

LDH released from BEAS-2B cells was measured after exposure to dust for 24 hours. Figure 10 shows that low concentrations of both types of indoor dust did not cause cell membrane damage.

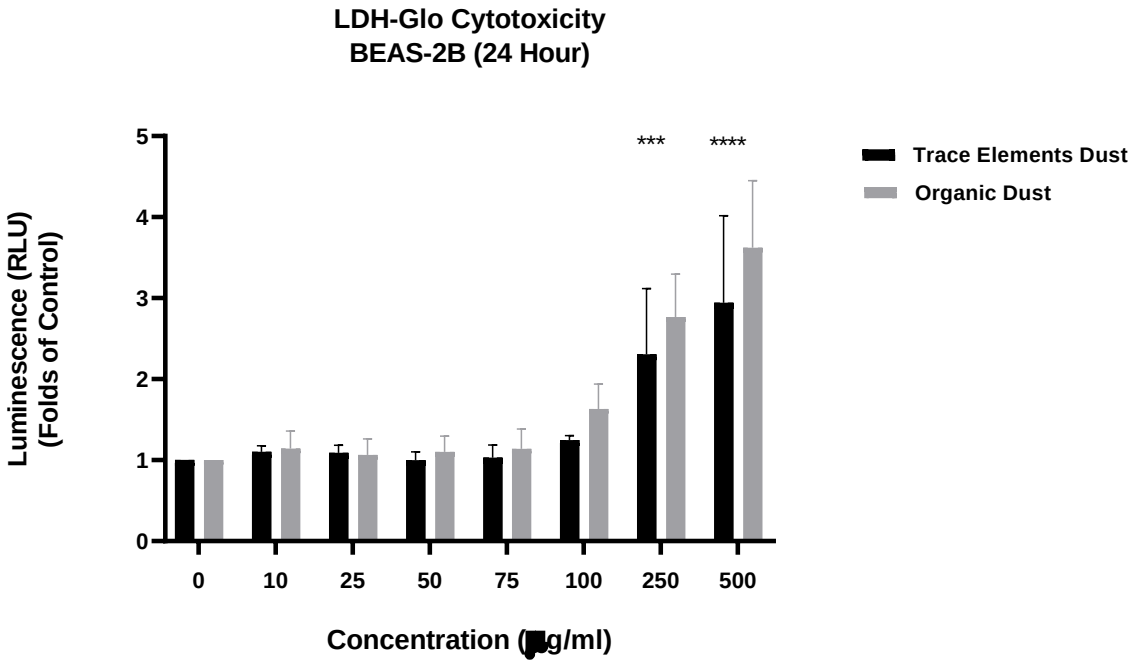


Figure 10: Concentration-dependent cytotoxicity (LDH release) in BEAS-2B cells after exposure to Trace Element Indoor Dust and Organic Contaminants in House Dust (0, 10, 25, 50, 75, 100, 250, and 500 µg/ml) for 24h. The data are expressed as mean + SD fold change of control of three experiments.

On the other hand, at 100 µg/ml, the LDH release was slightly but not significantly increased. Higher dust concentrations (250 and 500 µg/ml) mainly affected cell membrane

damage. Compared with the untreated control, treatment with 250 and 500 μg/ml dust significantly increased the LDH release level by up to four times.

The impact of fetal bovine albumin (FBS) on experimental outcomes must be carefully considered. Serum-free media was used in this study to investigate the cytotoxicity of the dust because some components in the serum (such as albumin) can act as metal chelators, which leads to reduce the impact of dust on the cells (Sánchez-Pérez et al., 2009).

Indoor Dust Exposure Activates Apoptosis (Caspase-3/7)

To study the mechanism of BEAS-2B cell death, we compared the activation of caspase-3 and -7 after 24 hours of indoor dust treatment. By comparison, dust treatment resulted in increased caspase activity beginning at 75 μg/ml, followed by a concentration-dependent rise (Figure 11). A significant spike in caspase activity was noticed when 100 μg/ml concentration was used, followed by a decreased activity until it returned to the measured background level at 500 μg/ml concentration point.

These results suggest that for moderate concentrations of indoor dust, apoptosis is the main pathway of cell death, while exposure to high concentrations can promote other cell death mechanisms (necrosis).

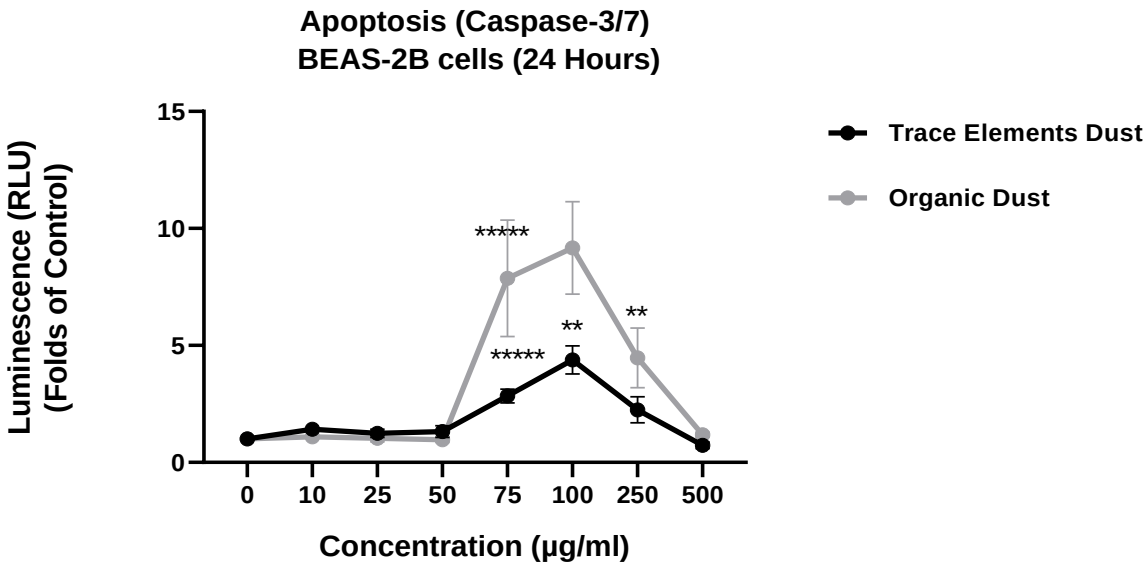


Figure 11: Caspase-3/7 activation in human lung epithelial cells after exposure to Trace Element Indoor Dust and Organic Contaminants in House Dust (0, 10, 25, 50, 75, 100, 250, and 500 µg/ml) for 24h. The data are expressed as mean + SD fold change of control of three experiments.

During regulated extrinsic or intrinsic apoptosis, caspase-3 and -7 can control several biochemical and morphological changes, including formation of apoptotic bodies and DNA fragmentation (Galluzzi et al., 2018). Apoptosis has a substantial role in the pathophysiology of respiratory diseases and lung inflammation (El Kebir et al., 2012; Pierce et al., 2007). Investigating if indoor dust cause apoptosis in lung cells could further recognize or understand respiratory diseases induced by dust exposure.

The increase of caspase-3/7 signal after treatment with the indoor dust suggests that the mechanism of toxicity is due to apoptosis induction. However, a decrease in caspase-3/7 signal is observed at higher dust concentration treatments with an increase in cytotoxicity marker (LDH) indicates an increasing number of dead cells and suggests cell death by the necrotic pathway. This response confirms that the dust exposure dose determines the type of cellular death mechanism in addition to the chemical composition

(Nel et al., 2001). These data support the earlier hypothesis that the same chemical can induce apoptosis at low concentrations and necrosis at higher concentrations (Elmore, 2007). For example, low-dose diesel exhaust particles can induce cell apoptosis (Yun et al., 2009), whereas high-dose has been reported to induce necrosis (Nel et al., 2001).

We used 50 and 100 μg/ml of both types of dust as the optimal concentrations in further experiments.

Indoor Dust Exposure Induces Intracellular Reactive Oxygen Species Generation (H_2DCFDA levels)

The most common reagent used for measuring intracellular ROS levels is 2',7'-dichlorodihydrofluorescein diacetate probe (H_2DCFDA), which undergoes oxidation by ROS to form a highly fluorescent green color.

Reactive fluorescent dye H_2DCFDA was used to detect ROS expression in human lung epithelial cells After exposure to 50 and 100 μg/ml of indoor dust for 24 hours. ROS generation was increased after exposure to both dust samples compared to the control (Figure 12).

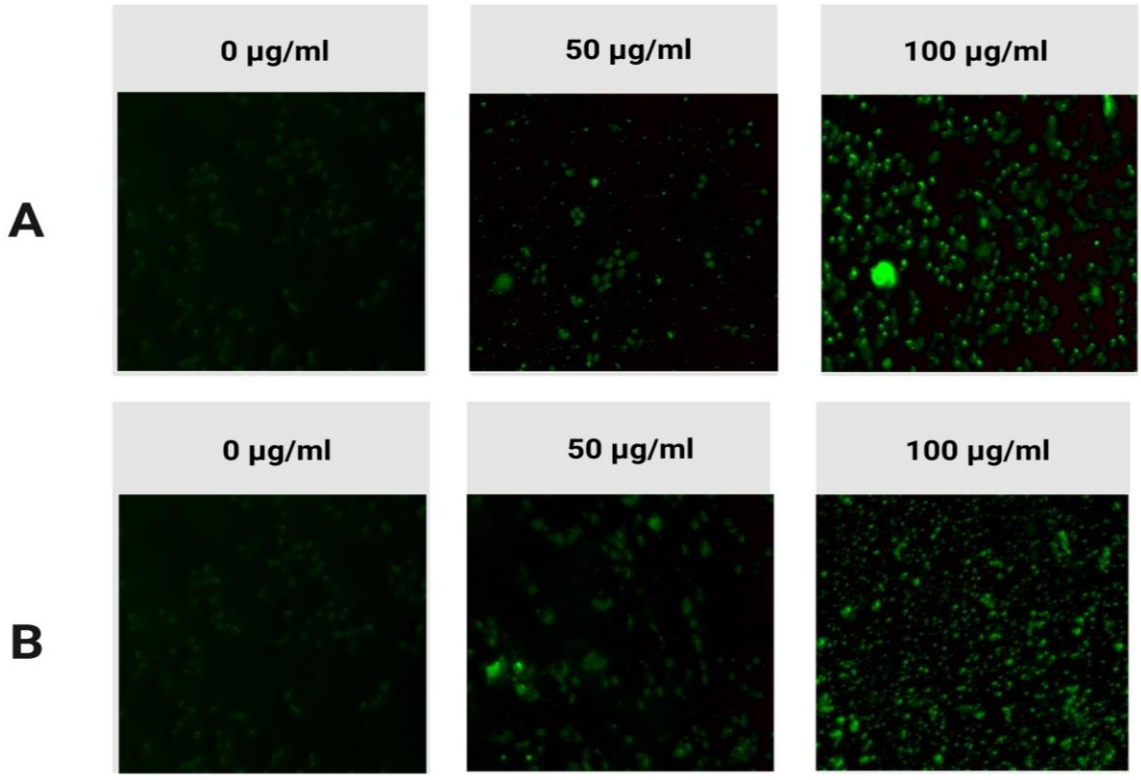


Figure 12: Indoor dust-induced oxidative stress in BEAS-2B cells after 24 hours exposure to 50 and 100 µg/ml of Trace Elements Indoor Dust (A), and Organic Contaminants in House Dust (B) and staining with H2DCFDA probe. Compared with untreated cells, the ROS (fluorescence intensity) increases with increasing dust concentration. Green fluorescent dots indicated ROS-positive cells.

Reactive oxygen species are chemically reactive molecules generated as a waste product of regular cell metabolism. Excessive generation of ROS can cause cellular oxidative stress, which is the toxicological mechanism that triggers the harmful impacts linked with exposure to air pollution and particulate matter (Chow et al., 2006a; Chow, 2006). A fluorescent dye (H_2DCFDA) was used to detect any increase in ROS generation in BEAS-2B cells after exposure to indoor dust for 24 hours. An increase in ROS generation was noticed after exposure to both dust samples compared to the control. These

findings indicate that cell exposure to indoor dust induced ROS production that possibly will cause oxidative stress and cell damage.

Indoor Dust Exposure Induces Extracellular Reactive Oxygen Species Generation (H_2O_2 levels)

H_2O_2 is a reactive oxygen species that can be measured as a cell marker for oxidative stress. After 24 hours of exposure to dust, H_2O_2 release is significantly increased compared with the control group (7.08 and 11.25-fold for Trace Element dust, and 6.01 and 8.91-fold for Organic Contaminants dust) after exposure to 50 and 100 µg/ml dust, respectively (Figure 13).

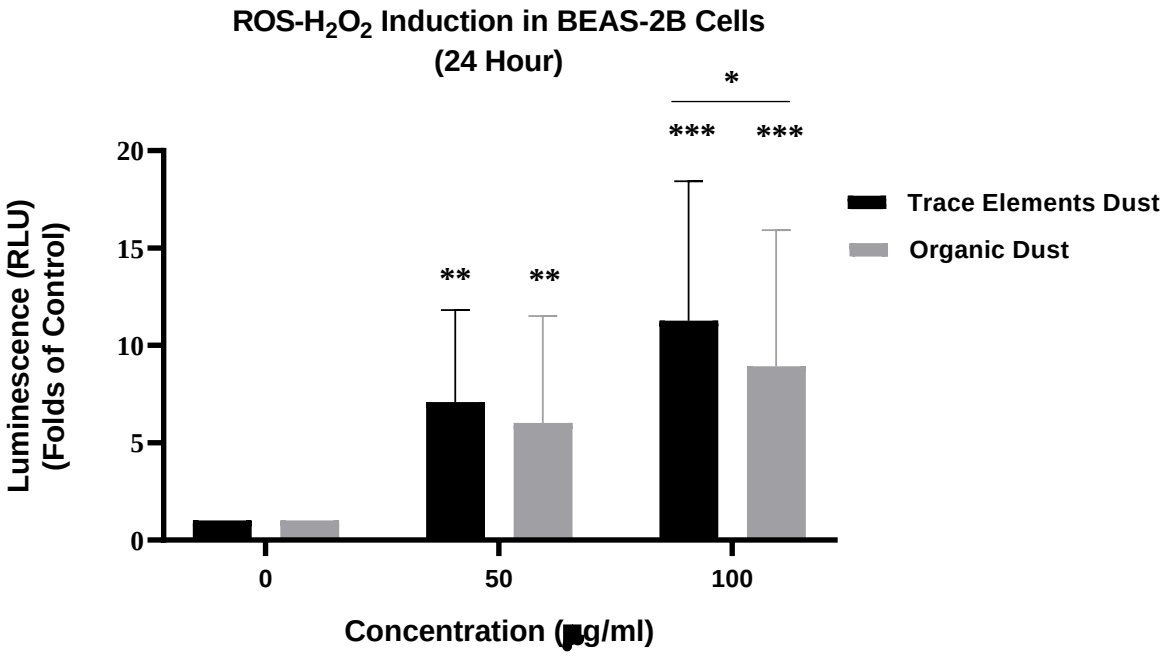


Figure 13: H2O2 release as a marker of oxidative stress in BEAS-2B cells after 24 hours exposure to 50 and 100 µg/ml of Trace Element Indoor Dust and Organic Contaminants in House Dust. The data are expressed as mean + SD fold change of control of three experiments.

Hydrogen peroxides (H_2O_2) were used as another cell markers of oxidative stress in BEAS-2B cells. H_2O_2 can be generated either by dismutation of superoxide anion or by spontaneous formation from molecular oxygen in peroxisomes. Regardless of its lower reactivity compared to other reactive oxygen species, hydrogen peroxide has an essential role in carcinogenesis because it can diffuse across mitochondria and cell membranes, resulting in a diverse functioning outcome and causing a variety of cellular damages, such as inflammasome formation, NFκB activation, and proinflammatory cytokines stimulation (Mates & Sanchez-Jimenez, 2000; Mittal et al., 2014; Ray & Husain, 2002).

Indoor dust caused a significant increase in H_2O_2 release after 24 hours of exposure to 50 and 100 μg/ml dust compared with the untreated cells. The H_2O_2 release potential for the trace metal dust was more than that of organic dust. However, the cell cytotoxicity was higher in cells subjected to organic dust in comparison to cells subjected to trace metal dust using the same concentrations.

Oxidative stress has a variety of effects on cells, such as the formation of pro-inflammatory molecules and structural cell damage. Screening compounds for their ability to modify hydrogen peroxide levels in cultured cells is beneficial since different ROS in the cell are interconverted to hydrogen peroxides, and because hydrogen peroxide is the longest-lived reactive oxygen species, an increase in hydrogen peroxide may suggest a general increase in reactive oxygen species (Vidugiris et al., 2015).

Indoor Dust Exposure Activates First Line Antioxidant Enzymes

To determine whether increased ROS generation was gone together with the deregulation of antioxidative enzymes' expression, western blot analysis

of SOD1, SOD2, CAT, and GPx was made after exposure to 100µg of Trace Metal Indoor Dust and Organic Contaminants House Dust (Figure 14).

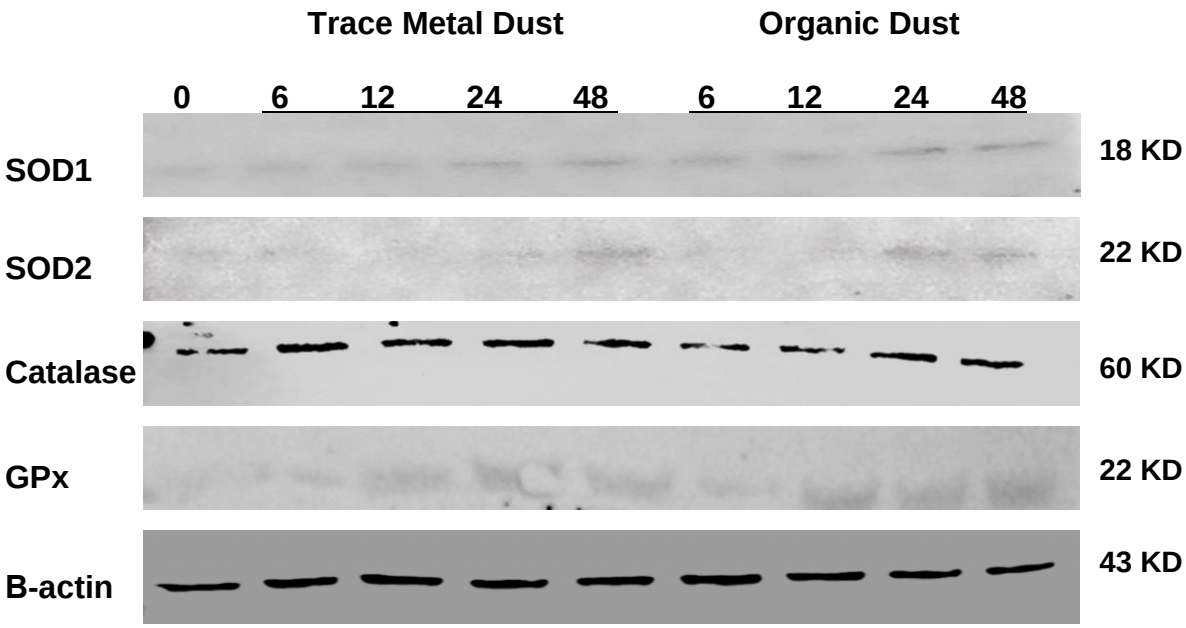


Figure 14: Time kinetics of antioxidant enzymes (SOD1, SOD2, CAT, GPx) activation in BEAS-2B cells exposed to 100µg/ml of Trace Elements Indoor Dust and Organic Contaminants in House Dust.

SOD1 was upregulated after exposure to both indoor dust types in a time-dependent manner (Figure 15), especially after 24- and 48-hour exposure (2.18 and 2.41-fold for Trace Metal Dust; 4.37 and 5.93-fold for Organic Dust).

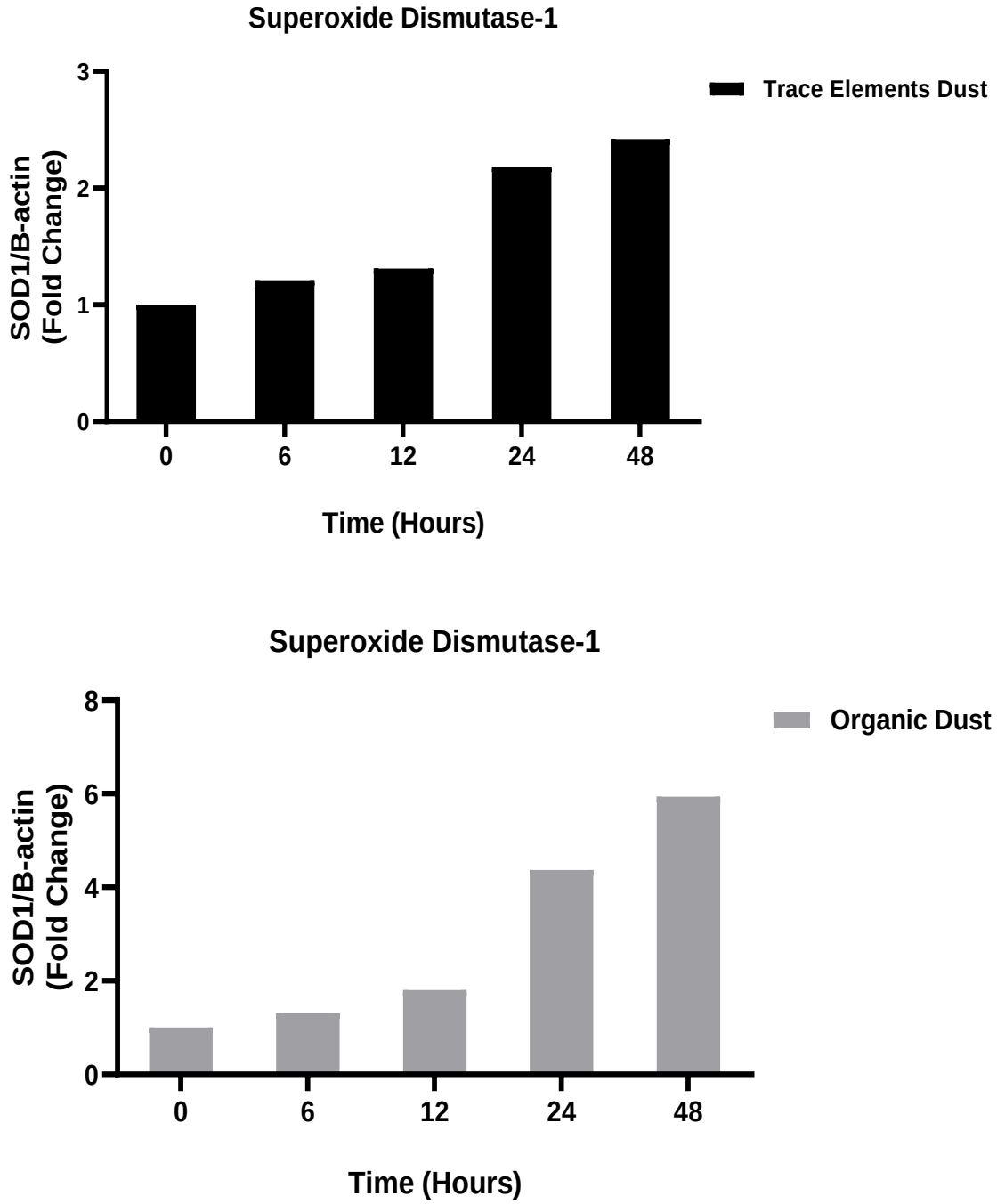


Figure 15: Graphical representation of the relative band quantification of superoxide dismutase-1 activation in BEAS-2B cells exposed to 100µg/ml of Trace Elements Indoor Dust and Organic Contaminants in House Dust.

SOD2 protein expression was downregulated after 6- and 12-hour exposure to the dust, whereas upregulated after 24-hour and 48-hour exposure (Figure 16), especially after

48-hour, showing more than a threefold increase for Trace Metal Dust, and more than fivefold increase for Organic Dust.

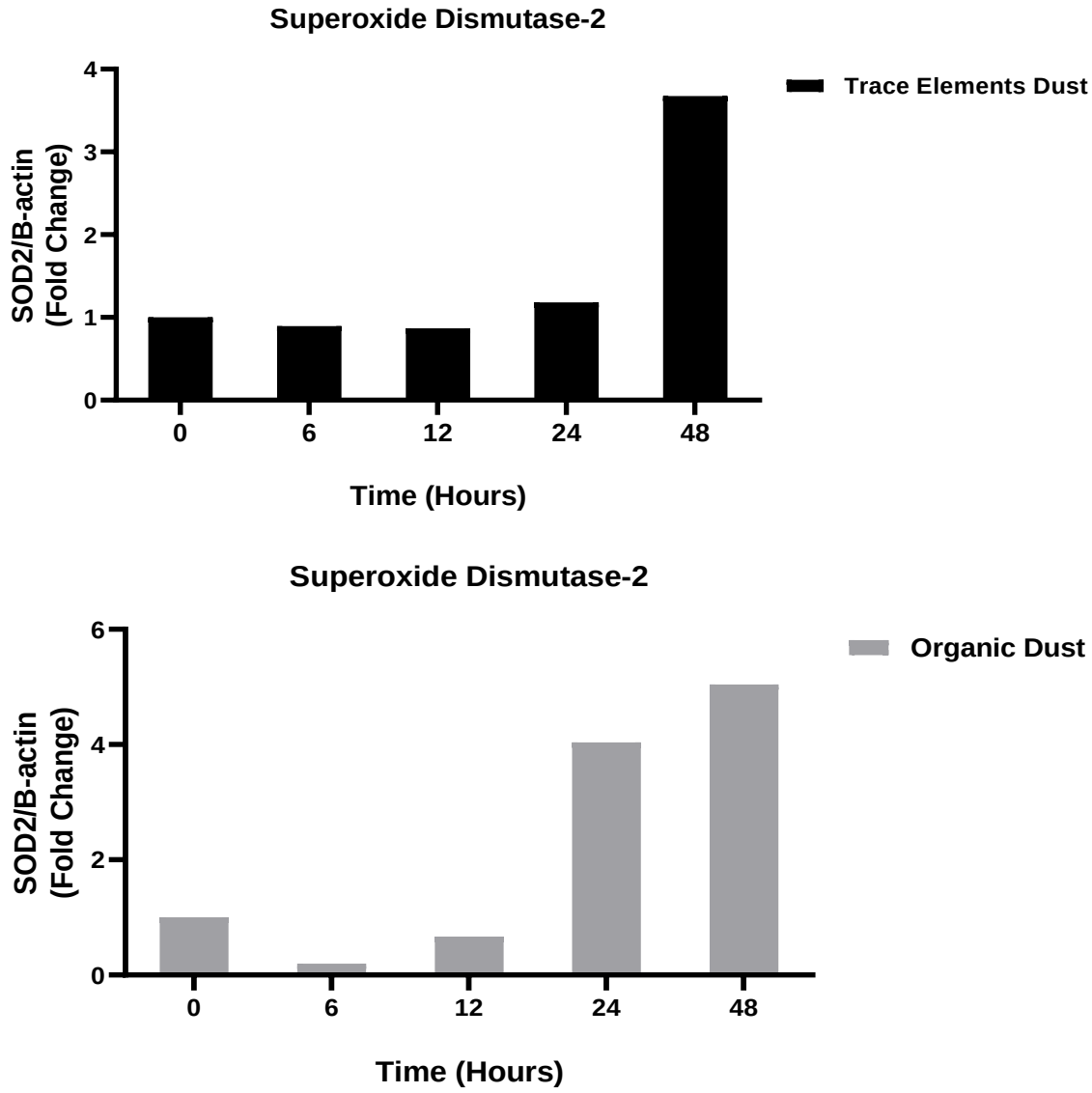


Figure 16: Graphical representation of the relative band quantification of superoxide dismutase-2 activation in BEAS-2B cells exposed to 100µg/ml of Trace Elements Indoor Dust and Organic Contaminants in House Dust.

Catalase enzyme protein expression was upregulated only after 6- and 24-hour exposure to Trace Metal Dust (Figure 17). Exposure to Organic Dust resulted in downregulation after 6- and 12-hour, followed by upregulation after 24- and 48-hour (2.1- and 2.51-fold change).

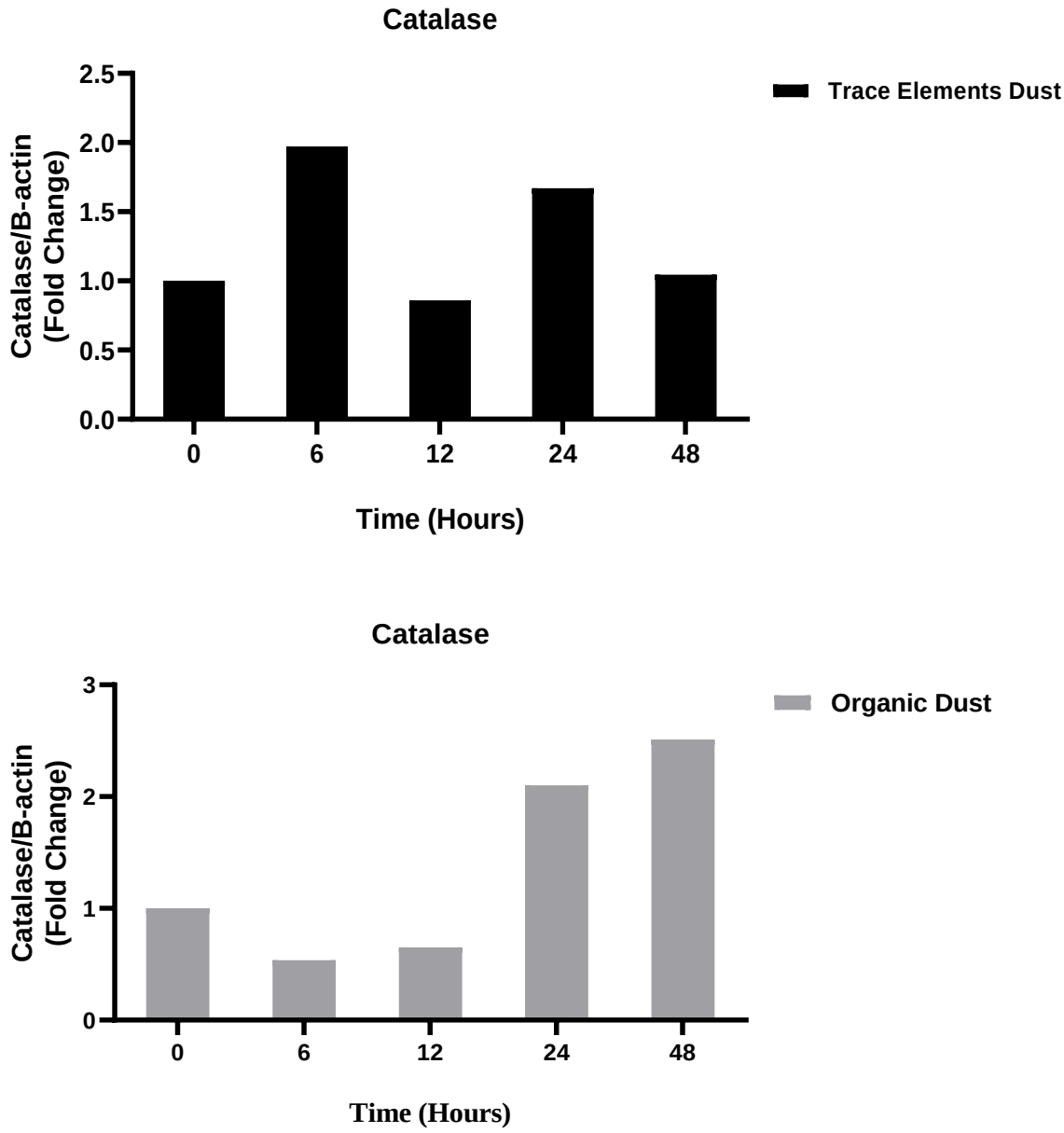


Figure 17: Graphical representation of the relative band quantification of catalase activation in BEAS-2B cells exposed to 100µg/ml of Trace Metals Indoor Dust and Organic Contaminants House Dust.

Glutathione peroxidase enzyme expression was intensely upregulated after exposure to both types of indoor dust, starting from 12-hour and continued thereafter (Figure-18).

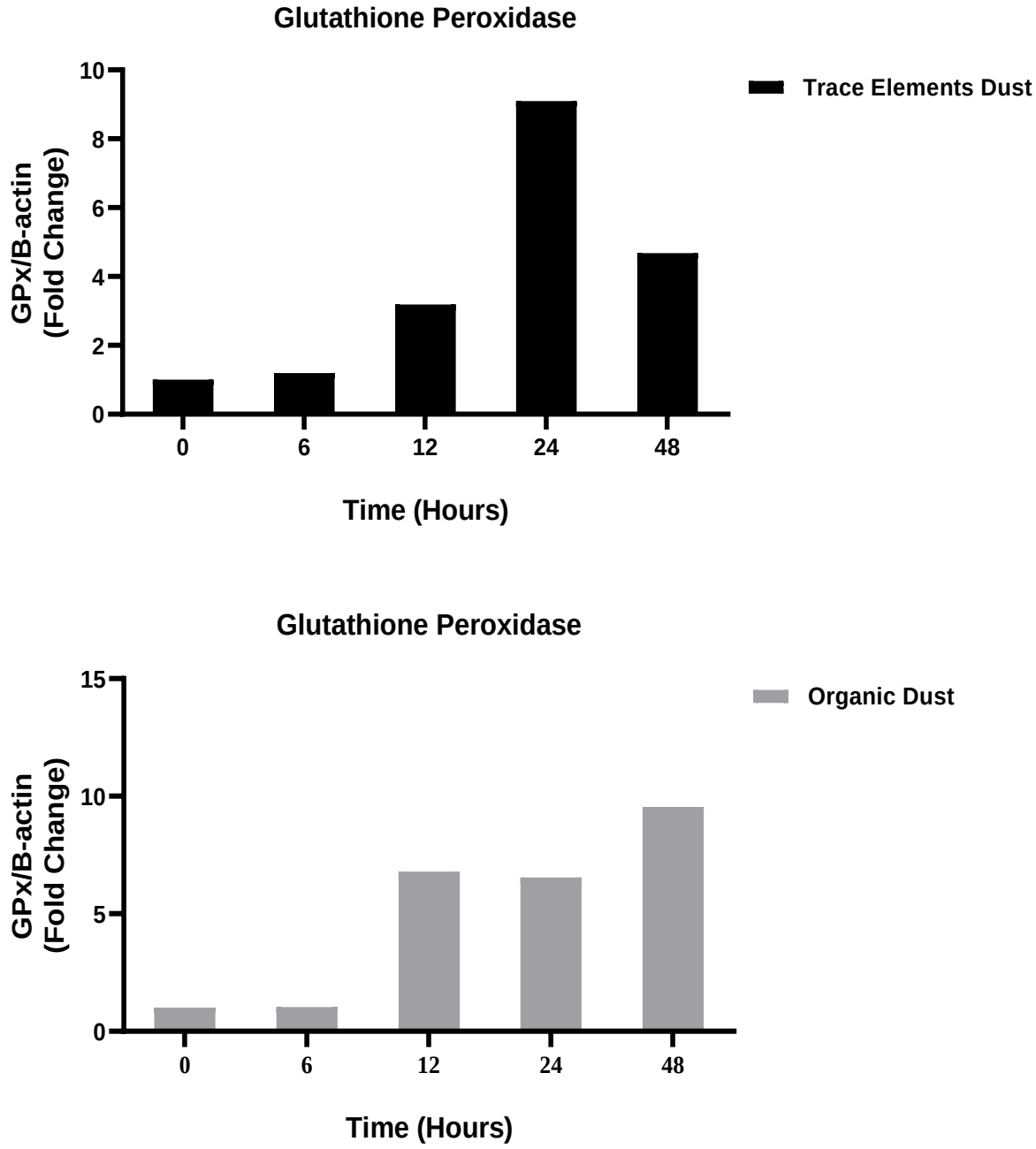


Figure 18: Graphical representation of the relative band quantification of glutathione peroxidase activation in BEAS-2B cells exposed to 100µg/ml of Trace Metals Indoor Dust and Organic Contaminants House Dust.

Western blot analysis of SOD1, SOD2, CAT, and GPx was used to determine whether increased ROS generation occurred together with the misregulation of the expression of these enzymes after exposure to 100µg of Trace Metal Indoor Dust and

Organic Contaminants House Dust. Our results show that indoor dust treatment can activate these antioxidant enzymes in a time-dependent manner.

Several experiments on primary antioxidant enzymes have revealed unpredictable performance. Some studies found that particle exposure can influence intracellular defense mechanisms by increasing antioxidant enzyme expression and activating the corresponding signaling pathways (Deng et al., 2013; Guerra et al., 2013; Messier et al., 2013; Pardo et al., 2015), while other studies found that particle exposure can downregulate antioxidant enzyme expression and activity (Davel et al., 2012; Delfino et al., 2008; Liu & Meng, 2008; Wang et al., 2015). The differences in these studies' findings can be correlated to differences in samples concentration and composition, in addition to the host's defensive capacity.

Indoor Dust Exposure Activates Inflammasome Caspase-1

Caspase-1 Glo Inflammasome assay was used to detect the activity of caspase-1 in BEAS-2B cells subjected to indoor dust for 24 hours. The results show that the Caspase-1 activation increases in a concentration-dependent manner when the cells are subjected to 50 and 100 μg/ml of the dust (Figure 19).

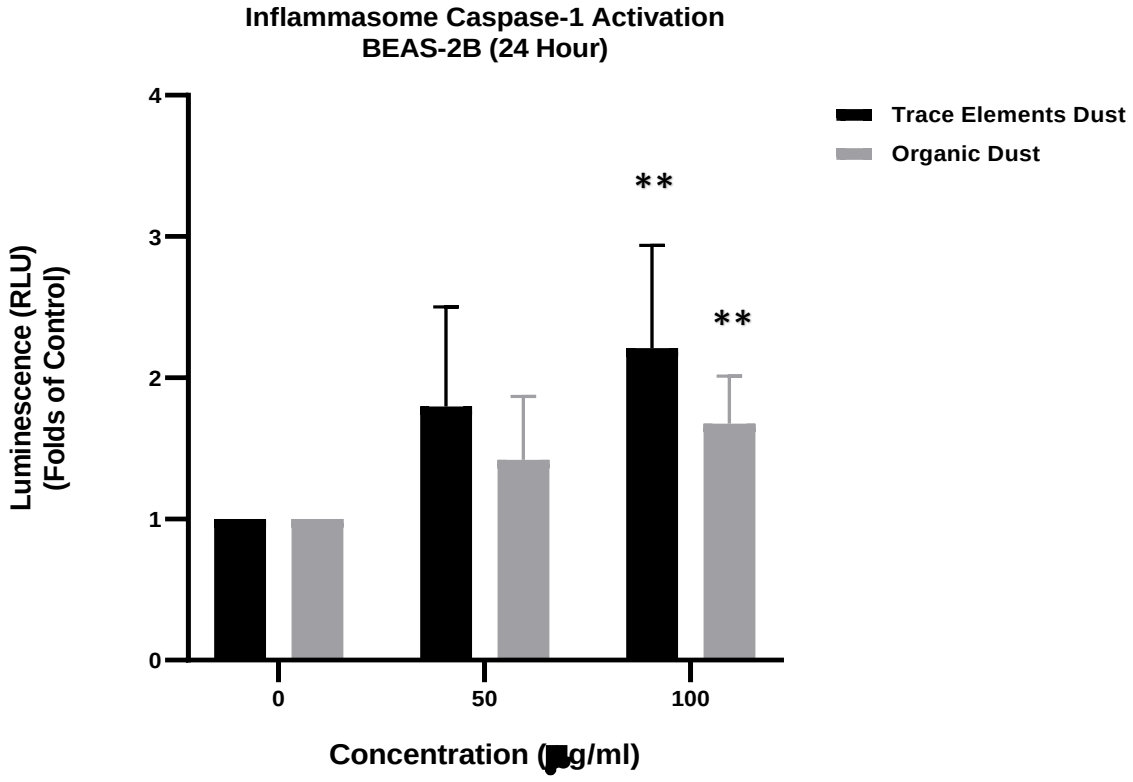


Figure 19: Caspase-1 Glo Assay revealed the caspase-1 activity stress in BEAS-2B cells after 24 hours exposure to 50 and 100 μg/ml of Trace Element Indoor Dust and Organic Contaminants in House Dust. The data are expressed as mean + SD fold change of control of three experiments.

Caspase-1 is an important part of the polyprotein inflammasome complex (Broz & Dixit, 2016). When it is active, it can further activate the pro-inflammatory cytokines IL1β and IL18 and lead to pyroptosis (a type of cell death that depends on inflammation) (Broz & Dixit, 2016; He et al., 2016; Mittal et al., 2014). Caspase-1 Glo Inflammasome assay was used to detect caspase-1 activity in BEAS-2B cells after exposure to indoor dust for 24 hours. The activity of caspase-1 was significantly increased in lung cells after exposure to indoor dust (50 and 100 μg/ml), indicating that pyroptosis is probably involved in the observed cell death.

According to reports, the particle's organic components seem to have a significant role in inflammation and oxidative stress after exposure to particles. (Baulig et al., 2004; Bonvallot et al., 2001). At the same time, metals adsorbed to particulate matter can also cause inflammation and oxidative stress (Kennedy et al., 1998, Zhang et al., 2008). This study found that inflammasome activation in cells exposed to trace metal dust was higher than in cells exposed to organic dust. Other studies have also shown that air particles with higher metal content and lower organic content can cause significant release of inflammatory mediators, complemented by more pronounced oxidative stress (Ghio, 2004; Hetland et al., 2005).

The regulation of inflammatory responses has been connected to oxidative stress, and recent evidence supports this progressively (Choi et al., 2010; Mittal et al., 2014). Superoxide dismutase-2 activation may be one potential correlation between ROS overproduction and inflammation. SOD2 can react with mitochondrial O_2• to create the less toxic byproduct (H_2O_2). Hydrogen peroxide can cross the mitochondrial outer membrane to reach cytosolic targets, resulting in NFκB activation, inflammasome development, and proinflammatory cytokine stimulation, among other functional outcomes (Mittal et al., 2014).

Indoor Dust Exposure Activates MAPK Signaling Pathway

To realize whether indoor dust activates the MAPK signaling pathway, BEAS-2B cells were treated with 100 μg of trace metals dust and organic dust, and the levels of phosphorylated JNK, ERK, and p38 were measured using western blot analysis (Figure 20). The results indicated that indoor dust activated both ERK and p38 kinase pathways in the treated cells.

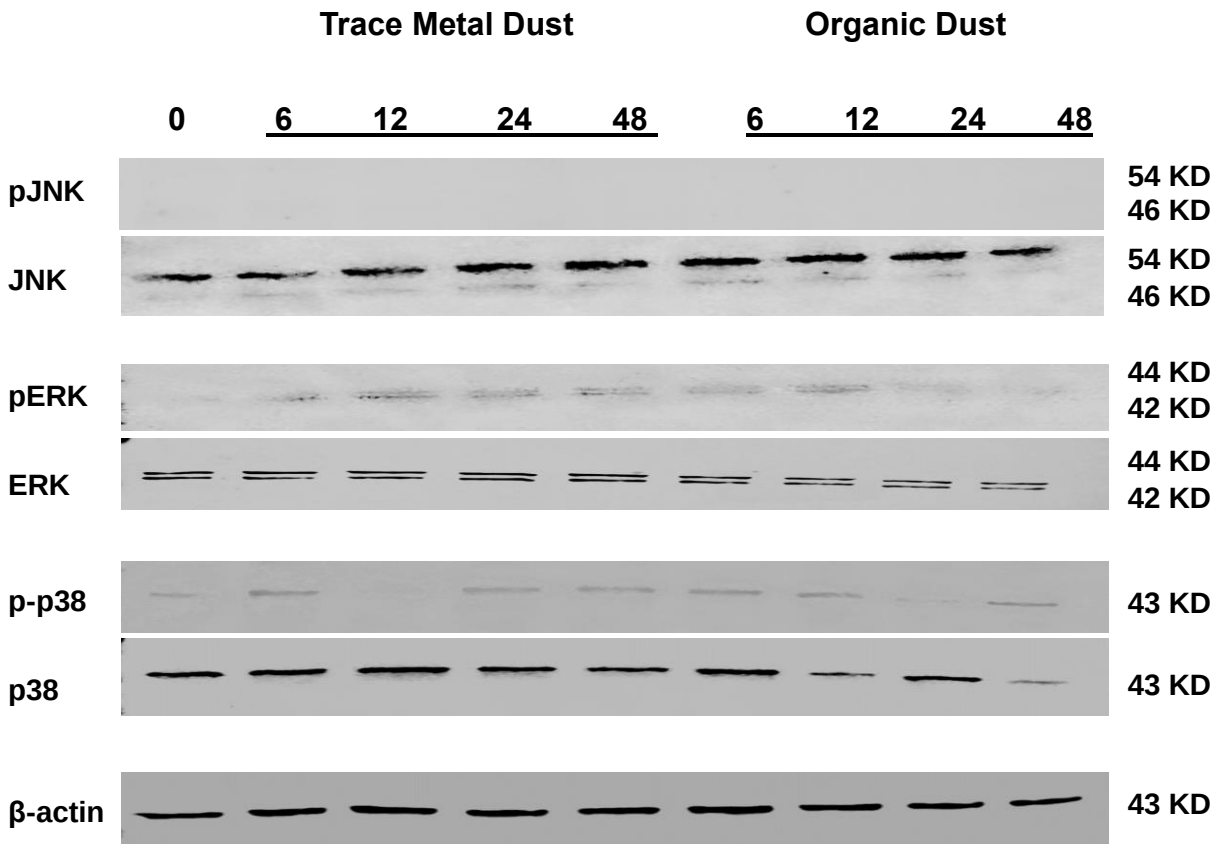


Figure 20: Time kinetics of MAPK (JNK, ERK, p38) phosphorylation in BEAS-2B cells exposed to 100µg/ml of Trace Metals Indoor Dust and Organic Contaminants House Dust.

Increases in phosphorylated ERK levels were noted at all times after exposure to both types of indoor dust (Figure 21), with the highest phosphorylation occurring at 12 hours (more than 11-fold change). After 24- and 48-hour dust exposure, the phosphorylated ERK levels were reduced compared to the levels expressed at 12 hours, but these levels still higher in comparison with control.

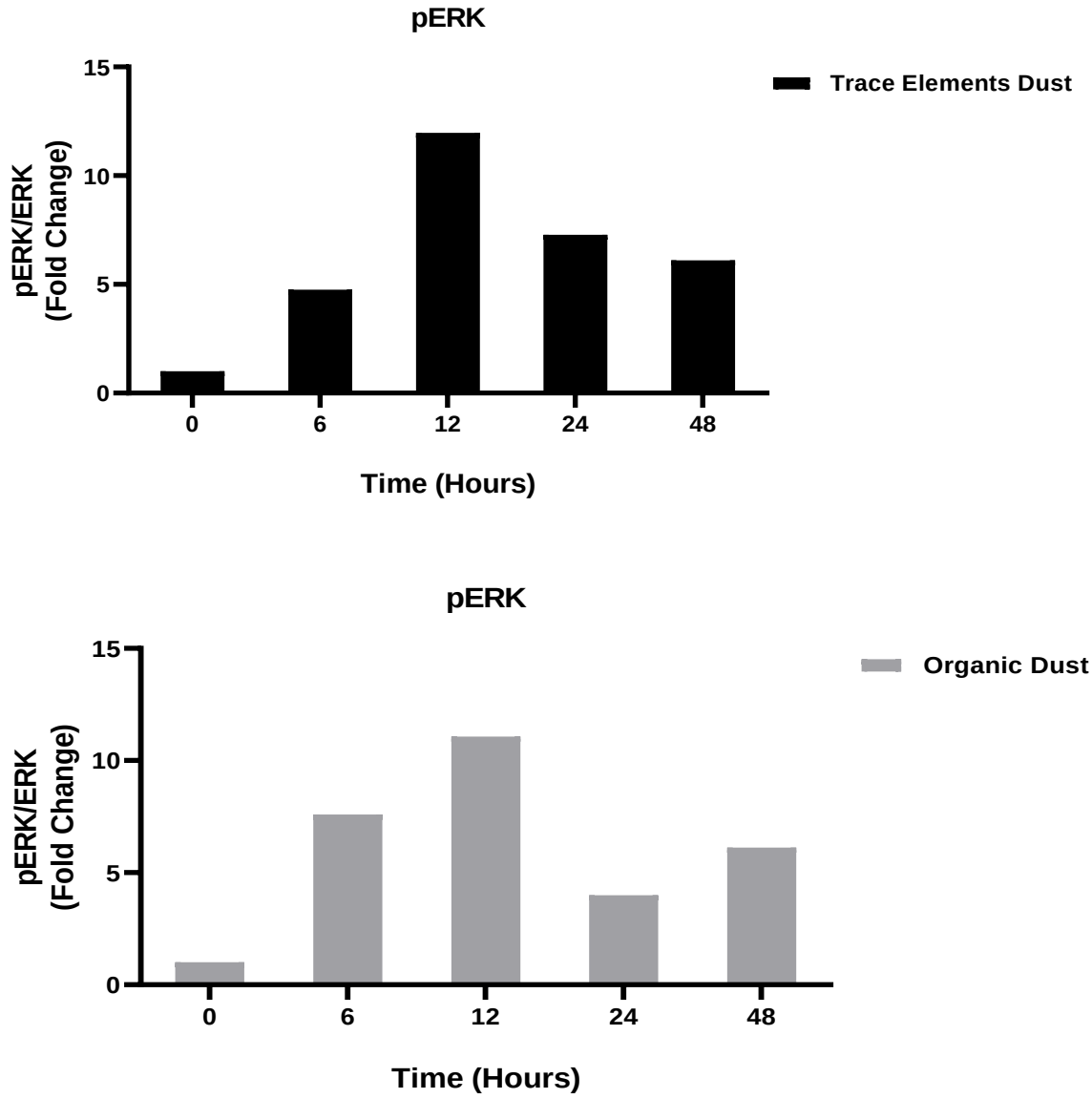


Figure 21: Graphical representation of the relative band quantification of ERK phosphorylation in BEAS-2B cells exposed to 100µg/ml of Trace Metals Indoor Dust and Organic Contaminants House Dust.

Increases in levels of phosphorylated p38 were seen at all times after exposure to trace metal dust, except after 12-hour exposure time, in which the phosphorylated level was decreased (Figure 22). After exposure to organic dust, p38 phosphorylation levels were

strongly increased over time, except after 24-hour exposure time, wherein there was an intense decrease in p38 activation.

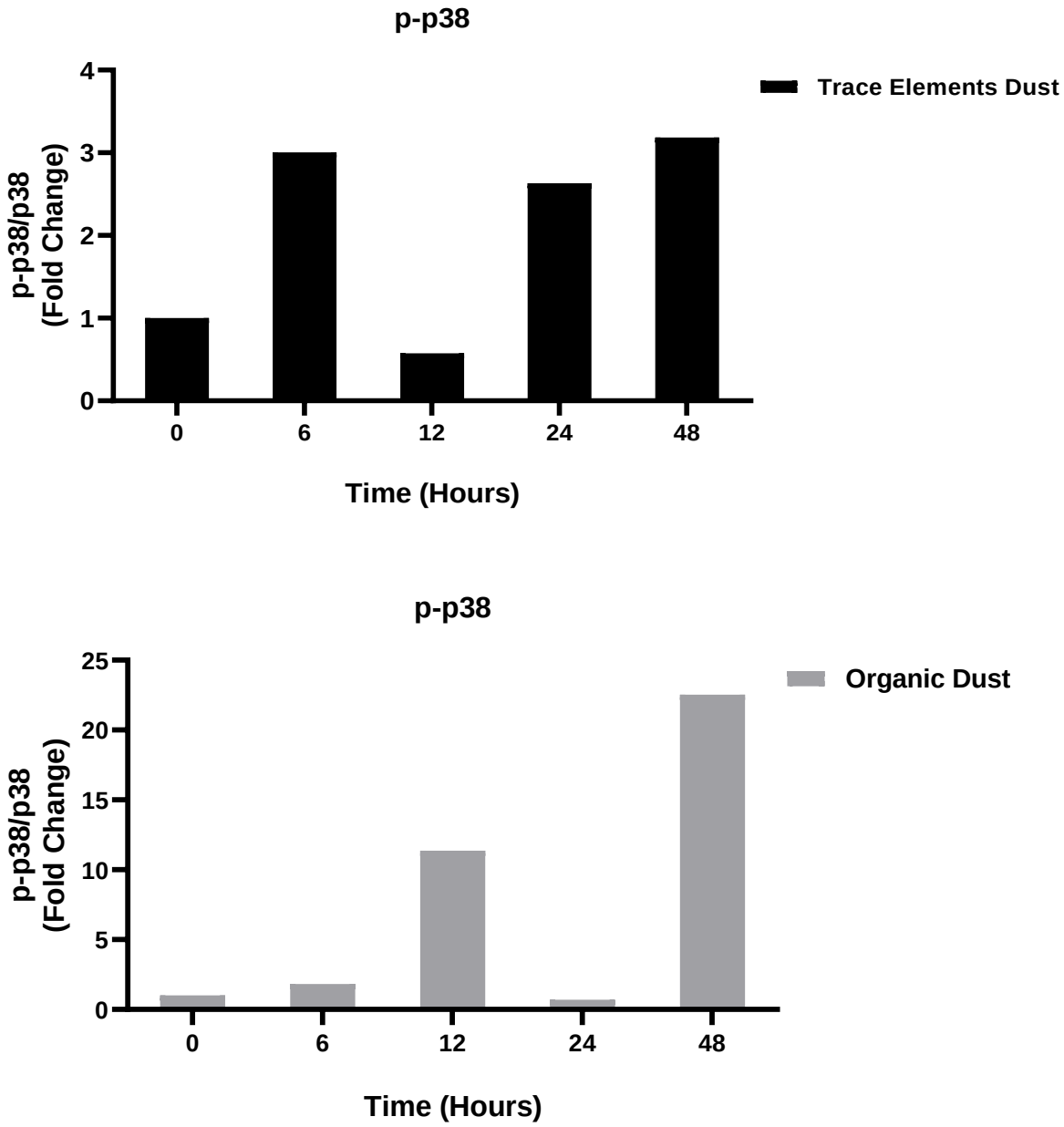


Figure 22: Graphical representation of the relative band quantification of p38 phosphorylation in BEAS-2B cells exposed to 100µg/ml of Trace Metals Indoor Dust and Organic Contaminants House Dust.

MAPKs are serine/threonine protein kinases. There are three MAPK pathways (JNK, ERK, and p38), which are associated with cellular growth, cellular stress, and inflammation (Fang & Richardson, 2005; Peng et al., 2018; Sun & Nan, 2016).

Environmental stresses and inflammatory cytokines strongly activate p38 MAPKs. Because of that, p38 MAPKs are referred to as Stress-Activated Protein Kinases (Cohen, 1997; Kyriakis & Avruch, 2001). The extent of p38 signal transduction play a crucial role in determining its biological effects. In response to the majority of stimuli, p38 activation occurs in minutes and it is transitory. This fact indicates that p38 acts as a bio-switch and must be down-regulated under basic or adaptive conditions (Takekawa et al., 1998; Takekawa et al., 2000).

The MAPK phosphorylation results indicate that indoor dust activates ERK and p38 kinase in BEAS-2B cells, but not JNK kinase. Comparable results were obtained through a study using urban dust, which showed the activation of ERK and p38 pathways in lung endothelial cells after exposure (Li et al., 2005).

P38 is generally connected with cell death (apoptosis) and inflammation, whereas ERK is involved in survival and proliferation (Kyriakis & Avruch, 2001; Roux & Blenis, 2004). Despite the fact that the P38 and ERK pathways appear to have opposing functions, several investigations have revealed extensive cross-talk between them (Shimo T, et al., 2007; Wang et al., 2006). The balance of ERK and P38 activation allows cells to decide whether to divide or stop the cell cycle, whether to promote or inhibit inflammation, and whether to live or die. The combined actions of P38 and ERK signaling result in diverse cellular outcomes, including cytokine secretion, cell proliferation, and cell death (Krishna & Narang, 2008; Kyriakis & Avruch, 2001; Roux & Blenis, 2004).

When the generation of ROS overdoes the potential of antioxidant proteins, they can induce the oxidative modification of certain MAPK proteins, leading to the activation of MAPK. ROS can activate the MAPK pathway by inactivating or degrading MAPK phosphatase (Guyton et al., 1996; Tournier et al., 1997). The influence of ROS on MAPK pathway activation depends on several factors, such as the antioxidant capacity of cells, and the concentration and production site of ROS (Son et al., 2011).

CHAPTER 5

SUMMARY, CONCLUSIONS, AND RECOMMENDATIONS

Indoor dust consists of a complex mixture of natural and man-made particulates that have a major role in human exposure to harmful contaminants. Its toxicity has been one of the most sensitive issues since it has caused millions of deaths worldwide. It is easier to get exposed to indoor dust particles because they are almost everywhere, originate from internal and external sources, and can last for a long time in the air or surfaces. It acts as a sink for various chemicals used indoors every day, and exposure to these chemicals can be through inhalation, ingestion, and dermal absorption.

Indoor dust can adversely affect human health, causing many diseases and disorders, such as respiratory diseases, cardiovascular diseases, neurological diseases, dermatological diseases, developmental disorders, immunological disorders, allergic reactions, endocrine disruption, obesity, and cancer.

Understanding the mechanisms of toxicity of indoor dust is a challenge because it is a complex mix of particles with different physicochemical properties and constituents. In an attempt to evaluate in vitro toxicity of indoor dust particles, we used two types of Indoor dust (Trace metals in indoor dust and Organic contaminants in house dust). We used BEAS-2B cells to examine dust exposure-related effects. This study focuses on integrating multiple viability and cytotoxicity assays in addition to reactive oxygen species and inflammatory response detection. Protein expression analysis of some signaling pathways was also considered to understand the toxicity mechanisms of indoor dust in lung cells.

The results show the dose-dependent toxic effects of indoor dust on BEAS-2B cells 24 hours of exposure. The quantitation of MTT reduction and live-cell protease activity (GF-AFC Substrate) were used to estimate the number of viable cells. Both assays showed a similar trend of significantly decreased cell viability after cell exposure to indoor dust. Lactate dehydrogenase (LDH) release as a marker for cells with a compromised membrane was shown to increase at higher concentrations of dust (100, 250, and 500 µg/ml). The activation of caspase-3/7 as an indicator of apoptosis, was shown to increase after exposure to 75 and 100µg/ml of dust (indicates that the mechanism of toxicity is due to apoptosis induction). However, a decrease in caspase-3/7 signal is observed at higher dust concentrations treatment with an increase in cytotoxicity marker (LDH) indicates an increasing number of dead cells and suggests cell death by the necrotic pathway.

Results from analyses using ROS generation detection markers showed that exposure to indoor dust causes a remarkable increase in ROS generation. The antioxidant enzyme levels (SOD1, SOD2, CAT, and GPx) show that Indoor dust exposure (100µg/ml) can upregulate or downregulate these enzymes in a time-depending manner.

Indoor dust exposure can also trigger the activation of inflammasome in lung cells, suggesting that pyroptotic cell death may has a role in indoor dust toxicity.

Western blotting results revealed phosphorylation of both ERK and p38 proteins, depending on the duration of exposure.

It's impossible to say which components of the studied dust samples are more responsible for the cellular adverse effects. Contaminants in indoor dust may interact with one another, leading to modification in the extent of the toxicity. Exposure to these contaminants together might result in stronger or weaker combined effects (additive,

synergistic, or antagonistic effects) that cannot be predicted or expected by analyzing the individual exposures separately.

This in vitro study focusing on the estimation of toxicity and potency of the indoor dust, and help to indicate any possible cellular health impacts. This might result in a plan to reduce the harmful health-impacting components in the indoor environment.

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