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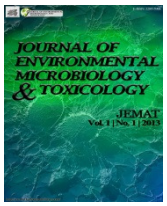

Phenol and Phenolic Compounds Toxicity

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Abstract

The present of phenol and phenolic compound pollutants are common problems faced by the global population due to natural and chemical process that comes from either industrial or human activity. Phenol levels exceeding the standard level in our environment is not a new issue, and every year reports on elevated levels of phenol in the environment are ever increasing. The study concerning to the phenolic compound was started in the early 1908 where researchers started to look for solution and are interested in phenol-related research due to its toxicity and ability to retain in environment for a long period. Higher level of phenol leakage within the environment can actually affects the whole ecosystem. A toxicological property of phenol has been contributed by the formation of organic and free radical species and also due to its hydrophobicity. The structure of phenol itself shows its reactivity which lead to its properties like persistence in environment, toxicity and the possibilities of carcinogenic properties toward living organism.

Introduction

Pollution is a long term environmental issue faced by the world which is now becoming a huge concern especially in Malaysia [1-3]. One of phenol's common xenobiotic polluted environments can exist through either natural process or man-made activities effluent/wastewater like mining, industrial and farming thus leading to bioaccumulation in high level of phenol amount in our ecosystem. Larger production or leakage of hazardous into environment can affect soil and groundwater quality [4, 5]. The huge increase of industrialisation in Malaysia for the past 20 years was the biggest contributions of this problem besides the natural process of plant decomposition naturally by fungi synthesising chlorinated phenol eg: tannin as secondary metabolite. Phenolic compound exist through many sources such as phenoxyherbicides eg: 2,4-dichlorophenoxyacetic acid (2,4-D) and phenolic biocides eg: pentachlorophenol (PCP) that present within the environment due to many human activities [6].

Phenol is a common industrial substance involve in especially the production of chemicals such as xylenols, oils, plastics [7], aspirin [8], antiseptics [9], pharmaceutical, oil refining [10], explosive, dyes [11], reagent in chemical analysis and leather and wood preservatives [12,13]. Industrial usage of phenols has been widespread since it can be used as an intermediate chemical in a wide range of applications, especially in the production of dyes, pesticides and drugs [14]. Phenol itself exists as a crystalline substance colourless in room temperature, and has hydroscopic properties in water and slightly in organic solvents that make them easily spilled or leaked into the surface water or inside ground water source [7]. Undergoing a variety of chemical reaction either at benzene ring or its hydroxyl group had made phenol to become a reactive compound. The industrial effluent which consist of mostly phenol and phenolic compound was quite resistance to biological decomposition due to the present of stable benzene ring. It can be accumulated and transported in the tissue before being excreted via body metabolic pathway, due to its persistence. Pollution caused by phenol or phenolic compound exist in environment either at atmosphere, hydrosphere or terrestrial area has been widely distributed and became a great concern [9]. The study on phenol has been started since the early 1908's [14] and has been extensively rose in the last decade for pollution prevention and cleanup process due to its toxicity and abundantly use in industries. The ability of phenol to accumulate in the organism has become an issue and a

great concern due to its well known toxicity [9, 15]. It was yet to become an important issue although many studies had been done because of its usage in many industries as an intermediate in their goods production.

This pollution occurs due to the rapid enhancement in population growth, urbanisation, the development of industrial sectors, the increasing of solid and hazardous waste discharged, and the effluent from wastewater treatment plant which leads to the discharging of higher xenobiotic levels especially phenol and phenolic compound [16-19]. Based on the few studies conducted by others, major pollutants that have been identified in water sources are phenolic compound, heavy metal, and pesticides [9,20]. It was estimated that on 2025, two thirds of world's population will live in countries with moderate or severe water shortages [21]. High levels of phenol in the environment can disrupt biological ecosystem and nutrient cycling [22, 23] because it was considered as a top list on the most hazardous chemical that is difficult to be removed [24] by human and other organism that makes them unable to tolerate it. Bioremediation method was chosen because it is one of the alternative ways to deal with pollution, compared to other processes due to the potential of forming harmful by-product and costly such as activated carbon adsorption and ion exchange [14, 25, 26]. This is why many studies were conducted using microorganisms such as algae, bacteria [14] and plants [27].

There are two types of phenol toxicity; acute and chronic exposure. Acute poison of phenol in human can be seen through symptoms such as dryness in throat and mouth, and dark colours of urine excreted due to the occurring of lipid peroxidation [28]. Chronic exposure causes several symptoms such as anderoxia, muscle pain, headache, gastrointestinal pain which will then lead to cancer [29]. Phenol is easy to be absorbed after being exposed via inhalation because it can present in the atmosphere as gaseous or particulate form or directly dermal contact. Phenol has the ability to irritate skin, and long term of dermal contact can lead to severe skin damage [22]. Oral accidental exposure to phenol may cause severe damage to the liver and kidney due to accident ingestion of 1 g phenol which is reported to cause fatality to human [30].

There are two major causes that can be related with the toxicity of phenol: hydrophobicity of the phenolic compound involved and the generation of organic and free species of radicals [6]. First, the hydrophobicity of solvent correlates with the logarithm of its partition coefficient in n-octanol and water (log P_{ow}). The toxicity of solvent influence by the value of log P_{ow} between 1.5-4.0 is toxic to living cells especially microorganism. Log P_{ow} value of solvent within that range has the ability to disrupt membrane structure thus impairing the important function [31]. Plus, reactive hydroxyl group can undergo substitution and also different chemical reactions such as chlorination in phenol structure which contribute to its toxicity. The benzene ring itself can also undergo several chemical reactions such as halogenations, alkylation, and nitrification. As an example, the presence of chlorine in phenol structure due to water treatment leads to the increasing of phenolic compound's toxicity and resistance in environment. The ability of phenol to persist in the environment depends on the properties of chemical groups attached to it and also on their position on the ring itself [6].

The importance of the study related to phenol degradation is to ensure and provide a safe place for the next generation in future especially water sources. In this review, we are elaborating a brief review on phenol research done in the world for the past decade. This review addresses issues on how the pollution occurs and also the toxicity of phenol and phenolic compound.

Phenol

Phenol, also known as hydroxybenzene, is an organic aromatic compound consists of the attached hydroxyl group to aromatic hydrocarbon group. Phenol exists in the environment through two major processes: chemical and natural. Naturally, it was formed by the part part of coal tar and creosote, decomposition product of organic matter, and as secondary metabolite in plant [27]. Phenol in either free or bound compound is found naturally in foods such as red grapes, cocoa, and tomatoes [32]. Phenol is also naturally produced during plant decomposition processes, usually in the form of intermediates such as ρ-cresol or lignin [27]. Phenol commercially available is in colourless, needle-like crystalline substances that easily dissolve in water and also organic solvents such as alcohol, glycerol and petroleum. Phenol is transparent and can easily mix with water at room temperature. It has a sweet odour and can be volatile when heated [7]. Chemically, phenol can be produce through the oxidation process of toluene, and the heating of monochlorobenzene together with sodium hydroxide [14]. High phenol concentration in water (100-1000 µg/L) can cause unpleasant odour and taste, and leads to carcinogenic problem whenever it presents in wastewater because it can react with chlorine to form chlorophenol and it is toxic to organism that can make it persistence [33].

Phenol can also vaporise easily making it widely present in the atmosphere. Phenol is considered as priority pollutant because it is harmful to human even in a small amount [34]. The inhalation of phenol within the atmosphere due to combustion product in air from natural process, residential wood burning, car exhaust and cigarette smoke, photooxidation of benzene during forest fires, ingestion of smoked food or occupational exposure. Phenol is a reactive substance due to presence of hydroxyl group. It will be substituted or undergoes other reactions to become phenolic compound after it is released into the environment, especially in water. The resultant from the reaction was phenolic compound such as chlorophenols, methylphenols, and alkylphenols that are more toxic, more recalcitrant, and persistence than phenol.

Phenol pollution

Environmental pollution is a worldwide problem that is faced by developing and developed countries over the year [35]. Phenol is the most utilised chemical with its production that reach around 3-billion pounds annually in United States, while 6-billion pound worldwide. It was proven at the United States that phenol was at the top 50 of the most chemical produced per year for the majority of the housing and construction industries [32]. Human activities are the major contributor to phenol pollution in the environment; especially in soil because its mobility

was limited than in an aqueous environment due to high adsorption onto solid surfaces [32, 36]. Soils areas within sawmills are usually highly contaminated with phenolic compounds because they are commonly used to produce wood preservatives [27]. Phenol has been used in industry since 1860s [14].On the early 19th century, it has been used in production of basic plastic resin before other products was invented such as dyes, chemical intermediates, and aspirin. The major use of phenol is for the production of phenolic resins, the synthetic polymers for construction, automotive, and appliance industry, the production of bisphenol A normally use for plastics manufacturing [37], and caprolacteam for synthetic fibre and nylon. In medical application, phenol is used in the production of general infection, slimicide, lotion, ointments, mouthwashes, and salves, while its minor use include s the production of paint, tanning dyes, lacquers, perfumes and ink [38-40].

The vast researches reported for the last decade clearly shows an increasing interest in research either in-situ or ex-situ for wastewater treatment and contaminated soil related to the degradation of phenol by variety pure or mixture of microorganisms been isolated due to its ability to degrade organic pollutant into non-harmful by-product to control pollution [14, 41, 42]. Governments have also created laws regulating the phenol level in drinking water and effluents discharged from factories as pollution prevention action in order to monitor, control and regulate it because it has been classified as an important contaminant [15, 43]. In each country, laws and acts have been created to observe the level of allowable metals present in effluent and water bodies. U.S. Environmental Protection Agency (US EPA) and World Health Organization (WHO) have set a guideline of 1 μg/l to regulate the phenol concentration in drinking waters [44]. The WHO priority of chemical pollution was given according to toxicity, persistence, mobility, and bioaccumulation ability [4]. European Council Directive has set up a limit of 0.5 μg/L in order to control the phenol concentration in drinking water [45], while Japan Ordinance No 15 law [46] permitted the phenol level of 5 mg/L in water source. UAE also limit the concentration of phenols in industrial effluent to the environment to 0.1 mg/L [47]. At Argentina, law 24051 of hazardous residues was established and the level of phenol in drinking water is limited to 2 µg/L [48]. In Malaysia, Department of Environment (DOE) has restricted the standard amount of pollutant that should be presented and the standard effluent discharge by industries [49] since phenolic compound is a ubiquitous compound found in factories effluent [16, 50, 51].

Phenol pollution also comes from different sources such as runoff from point sources, effluents discharged from the petrochemical industries [52] and from agricultural land. There are many reported cases of phenol contamination worldwide [4, 21, 53] and also in Malaysia [1, 2]. However, phenol pollution from nonpoint sources where xenobiotics have accumulated is even more concerning. Pollution can exist in various physical states, such as in liquid form came from the leakage of sewage effluent or factory effluent, or in solid form which came from water runoff or heavy raining. It was commonly used as disinfection for a few decades [7]. According to Philips and Bode, 2004, pollution related to water sources posses a major impact on human and ecosystem. The movement of pesticides from one point to another has been studied [53] because the compound often contaminates soil and groundwater especially man-made pesticides that usually persistence in soil such as organophosphate and organochlorine which has became a great threat to human and environment [55, 56]. Phenol can also contaminate soil and food through water [57], as it can be desorbs from the soil sediment in water source and re-enters the water phase where it can accumulates fish and harm other aquatic organisms [58]. More research focused on terrestrial and hydrosphere system has been made due to high probability of organism being affected by spills or leaks from pipelines to groundwater [59] or through atmospheric precipitation. There are various types of pollutants that also exist in water such as heavy metals, pesticides besides phenol and its derivatives [9] in wastewater. Table 1 shows IWK standard effluent which was listed that followed by factories and other sector that involved in the production of hazardous metal waste/effluent [49].

Table 1: The level of chemical allowed in IWK effluent in standard a) residential area, and standard b) industrial area.

Parameter	Unit	Standard effluent	
		A	B
T	˚C	40	40
pH	-	6-9	5.5-9
BOD	mg/L	20	50
COD	mg/L	50	100
Suspended solid	mg/L	50	100
Mercury	mg/L	0.005	0.05
Cadmium	mg/L	0.01	0.02
Chromium $^{(+5)}$	mg/L	0.05	0.05
Arsenic	mg/L	0.05	0.1
Cyanide	mg/L	0.05	0.1
Lead	mg/L	0.1	0.5
Chromium$^{(+3)}$	mg/L	0.2	1.0
Copper	mg/L	0.2	1.0
Manganese	mg/L	0.2	1.0
Nickel	mg/L	0.2	1.0
Tin	mg/L	0.2	1.0
Zinc	mg/L	1.0	1.0
Boron	mg/L	1.0	4.0
Iron	mg/L	1.0	5.0
Phenol	mg/L	0.001	1.0
Free chlorine	mg/L	1.0	2.0
Sulphide	mg/L	0.5	0.5
Oil and grease	mg/L	Not detectable	10.0

Toxicity of phenol and phenolic compounds

Phenol is considered as the main concern pollutant because of its harmful and toxic effects, and can be accumulated in living organism. Due to this concern, the level of phenol in drinking water and effluent has been also limited by international act and each country has proposed many profit and non-profit agencies such as EPA, and WHO. Phenol exposure cause by either directly or accidently exposure can disrupt the metabolic system in microorganism, human or animal. Phenol was also produced in a very small portion during the catabolism of protein by the bacterial interaction inside intestine and excreted out independently. Phenol can enter living organism through three different routes: dermal contact, ingestion, and inhalation [7]. Microorganisms which abundantly exist in environment were prone to be exposed to phenolic pollution which leads to many studies in order to find variety of species that is able to acclimatise, utilise and to develop mechanism to mineralise it into a non harmful substance [60].

Microorganism is important in aquatic ecosystem as the producer that involved in maintaining web chain and nutrient cycle in earth. In the past decades, many researchers are aware of the possibilities of phenol tolerant organism needed in the future especially to obtain non-polluted water sources, thus many various types of microorganisms isolated eg: yeast, fungus, bacteria were found that can help in the degradation of phenol in environment [10, 23, 29, 61-70]. According to Nwanyanwu and Abu, 2013 [71], phenol can affects the metabolic process of microorganisms and other organisms which can leads to death if they are unable to acclimatise it. The toxicity of phenol to human and animals also makes the removal of phenol or phenolic compound from the environment to become crucial. Table 2 shows different types of bacteria found for phenol degradation. From the table 2, it clearly shown that phenol pollution has already became a huge concern for the past decade, with pseudomonas sp being the main organism that can utilise phenol as a sole carbon [108]. Many methods were proposed in order to degrade phenol or phenol derivative substances in either biologically or chemically. However, due to the low cost and also the environmental friendly nature of biological method, biological method has been said to be commonly used by researcher. The recent studies done by researchers show the mixture of bacteria culture have a higher potential to achieved higher degradation rate in removal of phenol in high polluted area [24]. Microorganisms were able to acclimatize the presence of toxic organic compounds by a whole cascade of adaptive mechanisms that is related to the changes of the membrane composition. The toxicity of phenol and its derivatives always associated with their ability to disrupt the structure of membrane permeability and its barrier thus causing cascade effect which leads to the imbalance of intracellular cell environment, and the disturbance in its function can finally results in the cells' death [9]. It was found that the action of toxicity initially due to environmental stress factors lead in the changes happen in microorganisms [125] by the transition of saturation degree in membrane phospholipids cis-fatty acid into trans-fatty acid, and by the alteration of hydrophilic groups in lipids [126]. The toxicity of phenol depends on its aromatic ring where benzene ring itself can also undergo several chemical reactions such as halogenations, alkylation, nitrification, and polymerisation. Most phenol and its derivative are classified based on toxic activities. According to Boyd *et al.,* 2001 [127], the toxicity of phenolic compounds will also increase according to the number of chlorine being substituted in phenol. There are two major mechanisms in phenol toxicity-hydrophobicity of the phenolic compounds and the generation of organic and free species of radicals [128]. Main factors that alter the hydrophobicity are pKa (Ka is the compound dissociation constant) and P_{ow} (P is the octanol-water partition coefficient of undissociated acids) [31].

Table 2: List of microorganisms isolated around the world in past decade for phenol degradation in various methods applied.

Genus	Species	Concentration (mg/l)	References
Bacillus	*Bacillus cereus* mtcc 9817 strain akg1	<600	[72]
	Bacillus cereus mtcc 9818 strain akg2	<1000	
	Bacillus amyloliquefaciens strain wjdb-1	<200	[43]
	Bacillus sp. Strain phn1		[73]
	Bacillus brevis	<1750	[65]
	Bacillus sp. Sd3		[71]
	Bacillus cereus	<300	[10]
	Bacillus licheniformis		
	Bacillus megaterium	<400	[75]
	Bacillus pumilus	<400	
	Bacillus simplex	<1600	
	Bacillus cereus strain	<1000	
	Bacillus subtilis	3.705-11.98	[52]
Arthrobacter	*Arthrobacter* sp.	<300	[10]
	Arthrobacter citreus	20.7	[15]
	Arthrobacter sp. W1	<200	[62]
	Arthrobacter chlrophenolicus a6	0.1	[63]
Alcaligenes	*Alcaligenes* sp.	9.41	[76]
	Alcaligenes odorans	3.705-11.98	[52]
	Alcaligenes faecalis	<1600	[77]
		<1400	[78]
		<77.9	[79]
Acinetobacter	*Acinetobacter* strain atcc 11171	<1000	[80]
	Acinetobacter sp. Strain pd12	<1100	[81]
	Acinetobacter sp. Bs8y	<1200	[40]
	Acinetobacter sp. Strain aq5nol1	<1500	[1]
	Acinetobacter calcoaceticus	<1200	[23]
		<2,000	[82]
	Acinetobacter baumannii	100-2790	[83]
	Acinetobacter sp. Xa05	<1000	[33]
	Acinetobacter sp. *Edp3*	<1000	[84]
	Acinetobacter lowffii	<2500	[85]
	Acinetobacter sp. *Rte1.4*	200-600	[86]
Rhodococcus	*Rhodococcus phenolicus* sp.	<750	[87]
	Rhodococcus ukmp-5m	<900	[88]
	Rhodococcus sp. Strain aq5nol 2 kctc 11961bp	<2000	[2]
	Rhodococcus ad049	<1000	[89]
	Rhodococcus opacus strain 1g	<750	[90]
	Rhodococcus pyrinidivorans	500-600	[91]
	Rhodococcus coprophilus	600-1000	[92]
Pseudomonas	*Pseudomonas* sp.	<600	[18]
	Pseudomonas spp.	<500	[93]
	Pseudomonas sp. Jf122	<600	[94]
	Pseudomonas aeruginosa mtcc 4996	<1300	[95]
	Pseudomonas sp. Tx1	0.5–20%	[96]
	Pseudomonas putida	<100	[44]
		<200	[97]
		<100	[98]

		<300	[99]
	Pseudomonas putida mtcc 1194	<1000	[100]
	Pseudomonas putida ccrc 14365	0.29	[101]
	Pseudomonas putida ly1		[102]
	Pseudomonas aeruginosa	3.705-11.98	[52]
	Pseudomonas sp. Sa01	<1000	[103]
	Pseudomonas pictorium atcc 23328	<200	[104]
	Pseudomonas aeruginosa	<2600	[105]
		<80	[106]
	Pseudomonas pseudomallei	<1500	[105]
	Pseudomonas aeruginosa ncib 950	100–500	[107]
	Pseudomonas fluorescene ncib 3756		
	Pseudomonas sp. Sd1	<1000	[71]
	Pseudomonas resinovorans strain p-1	<600	[108]
	Pseudomonas fluorescens pu1	99.88	[109]
Ralstonia	*Ralstonia eutrophe*	1	[110]
		<1000	[111]
	Ralstonia pickettii	25-200	[112]
Halomonas	Halomonas *salina*	300	[10]
	Halomonas sp. Strain ph2-2	<1100	[113]
Corynebacterium	*Corynebacterium propinquum*	3.705-11.98	[52]
	Corynebacterium glutamicum	0.79	[114]
Citrobacter	*Citrobacter freundi*	<100	[115]
	Citrobacter sp. Rw1	<1000	[71]
Brevibacillus	*Brevibacillus sp.*	<600	[108]
Achromobacter	*Achromobacter* sp. Strain c-1	<600	[116]
Brevibacterium	*Brevibacterium epidermidis*	<3000	[117]
Ochrobacterium	*Ochrobacterium* sp.	<304.9	[118]
Brevibacillus	*Brevibacillus* sp. Strain p-6	<600	[109]
Staphylococcus	*Staphylococcus* sp. Rw2	<1000	[71]
Citrobacter	*Citrobacter* sp. Rw1	<1000	[71]
Actinobacillus	*Actinobacillus* sp.	2497	[119]
Sphingomonas	*Sphingomonas* sp fg03	<1000	[33]
Norcardia	*Norcardia hydrocarbonoxydans*	<74.26	[120]
Streptococcus	*Streptococcus epidermis*	<200	[121]
Xanthobacter	*Xanthobacter flavus*	<600	[122]
Stenotrophomonas	*Stenotrophomonas maltophilia*	<500	[123]
Micrococcus	*Micrococcus* sp.	<500	[123]
Delftia	*Delftia* sp.	<500	[123]
Limnobacter	*Limnobacter* spp.	0.23	[124]

Toxicity strength factor such as reactivity is related to the easiness of electron movement inside the benzene ring from oxidising substrates through the action of oxidase enzymes such as peroxidise. The higher hydrophobicity and log P with low value of pKa, will increase the solubility and penetration across cell membrane, which also increase the possibilities of interaction with the cell or tissue structures, thus enchancing its toxicity. For the compound that has the same pKa value, the rate depends on side aliphatic chain. Besides that, the toxicity strength depends on the localisation of substituent atom in the compound. It is also related to the interaction of substituents that form a force or strain inside the conformation of aromatic rings. The substituent on ortho position has less toxicity compared to compound that is being substituted at meta position. Some other factors is, the hydroxyl group attached are reactive group that can easily dissociated and undergo different chemical reactions such as esterification, etherification, oxidation, and substitution. The presence of hydroxyl group at the ring is causing it to become sensitive to the oxidising agents thus undergoing another reaction [6]. The hydrogen atoms at the ring and hydroxyl group can also be substituted or eliminated. The ability of phenol to persist in the environment depends on the properties of chemical groups attached to it and also on their position on the ring itself [24].

After being exposed and absorbed via the permeability of membrane, phenol will undergo active transformation in the presence of oxygen by oxygenase in cytochrome p450, main component in the electron transport chain. In this reaction, toxic compound that can possibly formed are phenoxy radicals and intermediate metabolite such as semiquinones and quinine methides that are able to bind and damage DNA or protein in the cell. The amount for the formation of reactive oxygen species like superoxides radicle and hydrogen peroxide based on phenol reactivity, and the presence of reactive oxygen species enhance lipid peroxidation on membrane thus lowering its permeability and makes penetration to become possible inside cell organelle such as endoplasmic reticulum, mitochondria, nucleus and its component such as enzyme and nucleic acid [6, 14, 32].

Human health exposure

Phenol exposure can occur through occupation exposure, environment, contaminated drinking water or foodstuff, and the usage of phenol-containing products [7]. IARC classified phenols as group 3, while EPA classified it as group D which are not classifiable with regard to its carcinogenicity to human due to insufficient data on human and animal. The absorption, distribution and excretion process in human needs to pass through the various types of barrier and membrane using a variety of transport mechanism before being widely distributed. Transportation of toxicant in body depends on the molecular weight/shape, charge, lipid solubility, membrane composition, and membrane thickness. When it has been widely distributed throughout the body, phenol can go across placenta, brain, and even in human breast milk [32]. Based on Michalowicz and Duda, 2007 [6], phenol is mainly found to be accumulated in brain, kidney, liver and muscles and after two days, it will be excreted or undergo conjugation in detoxification process [14, 32]. Phenol is easy to be absorbed via inhalation because it is presents in the atmosphere in gaseous or particulate forms followed by direct dermal contact and ingestion. The exposure of phenol into the living body will cause various adverse effects. Biological effect is a response to dose in a molecule, cell or tissue. The significance of biological effects has not been confirmed whether it is an indicator or a precursor for subsequent adverse health effects. The other one is adverse effect that cause changes in morphology, physiology, growth, development or life span leads to the result of impairment of the body function to pay off additional stress or the increase in body vulnerability that makes the body becoming more prone to other harmful or toxic chemicals [32].

Phenol exposed through short dermal contact has the ability to irritate skin even at diluted solution (1-2%) [14] and prolong dermal contact can lead to severe skin damage [22]. Damage to the skin is due to the coagulation by reaction of phenol with amino acids containing keratin of epidermis and collagen. Acute exposure on dermal contact can cause burns due to its corrosive and irritating properties. Dermal exposure is often related to occupational exposure. Workers working with phenolic compounds as one of the basic chemicals especially in the agriculture or chemical factories have the highest potential to absorb phenol compared to worker in other industry. It can also causes necrosis, symptom of systemic poisoning, and transient CNS stimulation and depression leads to coma when it is exposed to skin [14]. Phenol exposure can affects human but also depends on individual tolerance, similar to the ingestion case, direct contact on dermal or inhalation exposures. Chronic exposure can cause onychronosis, skin irritation, and skin eruption. Catechol, an intermediate for phenol degradation product is also a strong toxin compound aside from phenol.

Other compounds such as chlorophenol can undergo fast absorption by skin and mucous membrane in the respiratory system, while pentachlorophenol and tetrachlorophenol dissolved in fats and are absorbed by skin [6]. Its accumulation occurred in the spleen, kidney, liver, heart, brain, and fat tissues. Phenol or phenolic radicals are able to couple with metabolic processes inside mitochondria, thus it may be possible for phenol to alter the whole function of organisms. Inside the cell, the toxicity of phenol depends on substrate encounter, localisation and cell proliferation stage, besides the cell location of phenol exposure such as hepatocyte in liver [32]. Different organ have different mechanisms to maintain its function, as an example, phenol exposure in liver involved conjugation of glucuronides, sulphates, aminoacids, and other substrates that protect cells from metabolite influences by detoxification process involving endogenous antioxidant species. Most of the absorbed phenol is excreted via expired air and feces [22].

Ingestion of phenol can cause serious kidney and liver damages [28]. Acute poison of phenol in human through ingestion can be seen through symptoms such as dryness in throat and mouth, nausea, vomiting, and diarrhea, while chronic exposure causes methemoglobinemia, haemolytic anemia, profuse sweating, hypotension, arrhythmia, pulmonary edema, tachycardia [14] and dark colours of urine excreted due to the occurring of lipid peroxidation [28]. Phenol exposure causes initial blood pressure elevation, progressively low blood pressure, and shock [14]. People that are living near to places contaminated with phenol are reported to have headaches, nausea, vomiting, and abdominal pain [22] especially pollution related to water sources such as drinking water.

The exposure of toxicants to living organism occurs through three different routes: dermal exposure, inhalation, and ingestion (Figure 1). Toxicological process of phenol exposure to body will undergo three phase before the effects on organism can be seen as a changes in many aspects. Pollution comes from different sources in environment eg: water either surface or ground, air, and soil before exposed to human through different routes. First phase in toxicity response is toxicokinetics where it is a reflection on how the body handles toxicant as indicated by the plasma concentration of xenobiotic at various time points. In this phase, most of the toxicant which enter body may be eliminated through excretion. After that, the toxicant are absorbed into living cells and evenly distributed before being metabolised by biological system. Eventually the toxicant enters the last phase, toxicodynamics. In this phase, toxicant entered has already alerted some metabolism cascade reactions such as negative feedback to maintain body function and protecting the body from harmful substance. Then if the toxicant is unable to be eliminated, it proceeds to the next phase. There are different mechanisms inside the body that respond to it which leads to changes in human metabolism that is called toxicodynamic phase. Toxicodynamics refers to the molecular, biochemical, and physiological changes due to the effects of toxicant or their metabolites in biological systems. This phase leads to the changes in biological and maybe leads to adverse effect in body either in a good or bad way.

Men are more prone to the occupational exposure where the highest occupational exposure documented came from methylphenols. Based on Michalowicz and Duda 2007 [6], it has been estimated that global exposure to 4-methylphenol affected around 600 to 1,200 thousands of workers. This mainly refers to worker who produces antioxidants, disinfectants, dyes, plastics, explosives, epoxy-resins, coal tar and steel industry. According to HPA, 2007 [22], persons that work in tyre and rubber

industry have increase mortality rate from ischemic heart disease for phenol-exposed worker compared to non-exposed worker.

According to HPA, 2007 [22], there are about 70-80% of phenol exposure through inhalation, followed by dermal exposure of 80%. Since density of phenol vapour that is heavier than water vapour, inhalation hazard are limited by lungs. Based on Basha *et al*., 2010 [14], when adult and children had been exposed to phenol vapour, larger intake may be inhaled by children due to phenol density, their physical characteristic which cause higher amount phenol that is inhaled in lower ground, and children lung has higher surface area: body weight ratio and increase volume inhaled per minute: weight ratio. Children are more susceptibility affected by corrosive agent due to the small diameter of air passages. The proportion of phenolic compounds that comes from the combustion of tobacco in 1 non-filter cigarette is about 60-140 µg, filtered by about 19-35 µg, and from 24-107 µg cigar in a closed area [32].

Workers in the dyeing industry is also affected by exposure to phenol mainly through inhalation routes. In Poland, there are about 8,000 workers that are chronically exposed to benzene derivative such as phenol or m-cresol during the processing of resins for glue, dyes, and fibre at high temperatures [6]. According to WHO, there are only limited data collected on the adverse effects of inhalation ina short period of time [22].

The formation of radical species like reactive oxygen species (ROS) can disrupt normal metabolism. According to Michalowicz and Duda, 2007 [6], the liver, lungs, and gastrointestinal mucosa are the main sites for phenol metabolism in human. Human body has the mechanism to alter balance formation of ROS from cellular activities and endogenous antioxidant such as glutathione, catalase, glutathione peroxidase, and superoxide dismutase which can be found in the organ. As shown by Bukowska and co-worker, 2007 [129], the exposure of red blood cell to 3-dimethylaminophenol (3-DMAP) causing the inflection of oxyheamoglobin concentration and the increase of Met-Hb. Hb^{2+} ion is ferrous ions located in erythrocyte is responsible for oxygen transportation. In the presence of superoxide anion species, Hb^{2+} was converted into met-Hb (Hb^{3+}) form that is unable to transport oxygen, thus alter the whole body process [32].

Besides, the presence of excess formation of ROS and other free radicals was responsible for alteration of protein, nucleic acid, lipid and other molecules. Thus, alteration of structure may cause the cell to disfunction and dead. Besides, it has been reported that phenolic compound known as endrocrine disruptor that interfere the balance of hormone in body for homeostasis, reproduction, development and behaviour. Many researches related to the pregnancy mother have been made. Based on the findings and reports by ASTDR on 2007 [130], it can be concluded from 20 breast milk sample, top eight phenolic compound can be found such as Bisphenol A (BPA), 4-tert-octylphenol (4-tOP), ortho-phenylphenol (OPP), 2,4-dichlorophenol, 2,5-dichlorophenol, 2,4,5-trichlorophenol, 2,4,6-trichlorophenol, and 2-hydroxy-4-metoxybenzonephenone (BP-3) with 60% BPA as the highest, OPP, and BP-3. Phenol can be usually detected in urine by the changes of its colour or ρ-DCB 2,5-dichlorophenol detection.

Plant, Animal and Aquatic Ecosystem

Phenol that presents in a very little concentration in water can be toxic to some aquatic species and human since the tolerance of the organism towards phenol might be different. This will cause the disruption in food chains in the marine ecosystem. It is possible that the exposure of main pathway through drinking water can significantly contribute to major health problems since human cannot survive without water. It has been proven that several compounds have been found to exceed World Health Organisation (WHO) standards such as copper, lead, chromium and uranium [131].

Water sources such as static water like ponds and moving water like lakes and streams are most likely to be polluted by the presence of ubiquitous compounds such as pesticides, which happens to be one of the phenolic compounds [9]. It has been proven by Tiryaki and Temur in 2010 [132] that the movement of pesticides is affected by the type of soils, drainage, pesticides properties, and natural phenomenon, type and frequency of rain. It actually has several ways to harm human and the ecosystem such as disruption of aquatic web chain, affected non-target organisms, entering, accumulate and causing toxicity to organism [133, 134] which can also affects higher food chain such as human by influencing the organs especially nervous system [135]. A few studies have shown that pesticides such as DDT, HCH, and endosulpan [136] can cause an increase number of cancer either through short or long term exposure [137, 138] and carbamate an inhibitor of cholinesterase [139].

The responses shown in animal that exposed to phenol via inhalation are causes myocardial injury (inhalation and dermal), pulmonary damage, liver damage, renal damage, neurological effects, developmental effects, and dermal effects. Based on HPA [22], acute phenol exposure to animals in laboratory via inhalation led to respiratory irritant, hyperaemia, and purulent bronchitis. Phenol exposures via ingestion are able to cause throat and oesophagus mucous membrane to become inflamed and necrotic, while dermal exposure can cause inflammation, oedema, and eczema as reported in many laboratory animals and in some cases will lead to death.

Phenol chronic administration in animal show changes in their pathological traits such as in skin, esophagus, lungs, liver, kidneys, and urogenital tract, and also in biological trait due to adverse effect. It occurs due to the lipid peroxidation of membrane exposure. Chronic inhalation exposure of phenol can cause guinea pig to show signs of inflammation, cellular infiltration, necrosis in liver, renal proximal tubule, intestinal fibrosis, pneumonia, and signs which are similar to guinea pig in rats and rabbits except there are no neurological effects such as muscle tremors and movement disturbance in rabbits, while rat liver enzyme level decreased [22]. As for the chronic effect of phenol exposure through ingestion (40-53.3 mg/kg) per day, it shows that pregnant rats have shown sign of dyspnoea when exposed by gavage, in rats exposed per day to 0-120 mg/kg died within 11 days when phenol exposure reach 120 mg/kg per day, while rat exposed to 40 mg/kg per day has thymus necrosis or atrophy. On the other hand there were no adverse effect shown in rats

(16-1694 mg/kg) per day and mice (25-2642 mg/kg) per day when exposed in drinking water for 13 weeks. Dermal phenol chronic exposure on mice (5 mg) in 5% (w/v) solution for 32 weeks shows sign of skin crusts, while skin ulceration in mice happen when exposed to 5 mg of phenol in 20% (w/v) solution. According to DEFRA, 2003 [32], bacterial mutagenicity shows a negative result, but several in-vitro mammal system phenol exposure has been reported to have a positive data which shows that there are interaction occurs that makes Committee on Mutagenicity of Chemicals in Food, Consumer Product and the Environment (COM) agreed to classify it as an in-vivo somatic cell mutagen based on bone marrow micronucleus test. According to Burlow and co-worker, 2007 [32], some phenolic compound are endocrine disruptor, while Bisphenol A is an androgen disruptor where it can alter mammary gland development in lab test when exposed, and can mimic estradiol hormone and alkylphenol such as nonylphenol which disrupt normal rat mammary gland development [32, 140-142]. Phenol can also come across placenta as reported by NTIS, 2005 [32], in which it can cause congenital malformations. According to HPA, 2007 [22], 7000 mg/kg per day phenol in drinking water is able to disturb normal growth, while at 8000 mg/kg per day can cause offspring death due to maternal neglect, 1000 mg/kg per day leads to death of offspring, 12000 mg/kg per day able to inhibit reproduction at all.

CONCLUSION

Together with the development of industrialization especially in developing countries, people have become more aware of phenol exposure that has lead to abundant research over the years. Despite being the top of the pollution list for several decades, its pollution is constantly being reported globally as its demand is also increasing. The risk of phenol pollution cannot be avoided therefore making the study of phenol degradation still relevant as phenol is a priority pollutant. Among all methods available, biological method seems to have the potential for phenol degradation in either anaerobic or aerobic condition that makes it the choice for researcher compared to other method such as physical or chemical method. Toxicity of phenol and its derivatives have been associated with their ability to alter structure of membrane and its barrier. It leads to the imbalance of the cell environment which results in the cells' death. The toxicity of phenol and phenolic compounds to organisms warrants further studies to mitigate phenol pollution in the environment and better understanding of their toxicological properties.

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