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Review Article

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Chrysene: a carcinogen and its microbial degradation

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Abstract: Chrysene is one of 16 poly aromatic hydrocarbons which are toxic pollutants of priority by USEPA (United State Environmental Protection Agency). It is a high molecular weight PAHs ((Polycyclic aromatic hydrocarbon) consisting of four fused benzene rings with solubility 0.006 mg/l. Chrysene and it's different isoforms such as 6-nitrochrysene (6-NC), 5-methylchrysene are carcinogenic and mutagenic. Dibenzo (def,p) chrysene (DBC) is by far the most mutagenic and toxic polycyclic hydrocarbon identified. Its metabolic activation leads to the formation of such toxic metabolites that binds to DNA causing mutations and ultimately tumor induction. Bioremediation is a promising technique for the complete removal of such hazardous compounds from the nature. This review discusses the various carcinogenic isoforms of chrysene, their processing in the living tissues, triggering of various carcinogenic activities.

Keywords: Chrysene, Carcinogen, Hydrocarbons, Bioremediation, PAHs,

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Chrysene is a colorless to white, crystalline solid. It is also known as benzo(a)phenanthrene. It is most often found as the gaseous by-product from the incomplete combustion of fossil fuel, wood, Coal Tar and Creosote. High environmental concerns due to its carcinogenic and mutagenic nature (Smith et al. 1989; Nwanna et al. 2006) compel us to look for innovative methodologies for its biodegradation. Chrysene oxidation occurs by incorporation of an oxygen molecule in an aromatic ring catalyzed by dioxygenases to a *cis*-dihydrodiol intermediate, which undergoes further catabolism results in complete mineralization (Hinchee et al. 1994). Dioxygeneses is thus a group of enzymes which play a key role in metabolism of PAHs i.e. catalysed the first ring opening step of aromatic hydrocarbon (including chrysene) and presence of catabolic genes encoding this enzyme in microbes is indicative of their role in biodegradation.

The ubiquitous distribution of polycyclic aromatic hydrocarbons (PAHs) in aquatic environments has long been of great concern for their potential hazards to human health via tropic transfer in aquatic food chains. PAHs tend to be bio-accumulated and biomagnified due to their lipophilicity and chemical stability. A broad spectrum of microorganisms had been found capable of degrading PAHs, and bioremediation based on microbial processes has been considered as a promising alternative to conventional technologies to remove PAHs from contaminated soils and waters (Dean-Ross et al. 2002). However, PAHs can be photochemically decomposed under strong ultraviolet light or sunlight, and thus a fraction of PAHs is oxidized during atmospheric sampling. PAHs can also react with ozone, hydroxyl radicals, nitrogen and sulfur oxides, and nitric and sulfuric acids, which affect the environmental fate or conditions of PAHs. While physicochemical processes means to eliminate PAHs from the contaminated site but they degrade the quality of soil. The biological treatment of soil contaminated with PAHs is more environmental friendly, financially affordable and adaptable choice. It has the potential advantages such as the complete degradation of the pollutants, lower treatment cost, and greater safety and less soil disturbance (Habe and Omori, 2003).

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Biodegradation aspects of Chrysene-

Bacteria and fungi are the class of microorganisms actively involved in the degradation of organic pollutants from contaminated sites. A number of bacterial

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species are known to degrade PAHs. Most of them, with biodegradation capability, are isolated from contaminated soil or sediments. Long-term petrochemical waste discharge site harbors bacteria capable of degrading PAH. Degradation of chrysene, a four ring High Molecular Weight (HMW) Polycyclic Aromatic Hydrocarbon (PAH) is of great environmental concern, being a carcinogen.

A variety of bacteria and fungi were isolated that are capable of degrading high molecular weight PAH chrysene (Table1). Chirag et al. (2011) observed that halotolerant *Achromobacter xylosoxidans* could degrade 40.79% of chrysene by employing Response Surface Methodology (RSM) using Central Composite Design (CCD) of Bushnell–Haas medium components. A Proposed catabolic pathway for the degradation of chrysene by *Pseudoxanthomonas* sp. PNK-04 was given by Anand et al. (2011).

Table 1 isolated microbe capable of degrading Chrysene (selected list)

Microbes	References
Alcaligenes faecalis	John et al. (2012)
Achromobacter xylosoxidans	Chirag et al. (2011)
Pseudoxanthomonas sp. PNK-04	Anand et al. (2011)
Bacillus sp.	Monika et al. (2010)
Pseudomonas sp.	Monika et al. (2010)
Polyporus sp. S133	Tony et al. (2009)
Mycobacterium parmense	Salvador et al. (2009)
Pseudomonas Mexicana	Salvador et al. (2009)
Paracoccus	Haimou et al. (2004)
Pichia anomala	Abd El-Latif et al. (2006)

Likewise *Alcaligenes faecalis* (John et al. 2012*), Mycobacterium parmense, Pseudomonas Mexicana* (Salvador et al. 2009), *Bacillus* sp., *Pseudomonas* sp. (Monika et al. 2010) and fungi *Polyporus* sp. S133 (Tony et al. 2009) were isolated from different sources and were able to degrade chrysene. This list is still incomplete. *Paracoccus* strain degraded anthracene, phenanthrene, fluorene, fluoranthene, chrysene and pyrene, as well as cresol compounds and n-alkanesas sole carbon source. This is the first report of a representative of the genus *Paracoccus* capable of degrading PAHs with such versatility (Haimou et al. 2004). A yeast strain AEH was isolated from oil contaminated soil and identified by analysis of 18S and 26S ribosomal DNA sequences as *Pichia anomala*. Strain AEH was capable of degrading naphthalene, phenanthrene and chrysene, singly, and benzo(a)-pyrene in combination. The yeast degraded 5.36 mg naphthalene l^{-1} within 2 days and 5.04 mg phenanthrene l^{-1} and 1.54 mg chrysene l^{-1} within 10 days (Abd El-Latif et al. 2006). These three strains may be useful for bioremediation applications of PAHs contaminated soil.

Experimental proof of carcinogenicity of chrysene

Humans are periodically and perennially exposed to environmental agents that inflict damage to their DNA. Physical agents such as UV or ionizing radiation, and some chemical carcinogens, can interact with DNA and elicit a change in its structure (Friedberg et al. 1995). The damage that results from exposure to these agents can interfere with normal DNA transactions, including replication (Hruszkewyez et al. 1992) and transcription (Tornaletti and Hanawalt 1999), and can be an initiating factor in tumor-genesis. Among the wide variety of environmental agents that interact with DNA of particular concern in human carcinogenesis is the class of chemicals known as PAHs. PAHs are formed as a by-product of inefficient combustion of fossil fuels, and are widespread environmental pollutants present in cigarette smoke, cooked meat, industrial effluents, and vehicle exhaust fumes (Harvey, 1991). Many PAHs are known to be potent suppressors of the immune response. It is generally thought that the immunesuppressive potential of PAHs is linked to their carcinogenic potency (White et al. 1994). White et al. (1985) demonstrated that carcinogenic PAHs suppressed the plaque-forming cell (PFC) response in female B6C3F1 mice while non-carcinogenic PAHs did not, and the rank order of immune-toxic potency matched nearly the rank order of carcinogenic potency. In their study, BaP (benzo[a]pyrene) (160 µmol/kg/d, subcutaneous injection, for 14 d) was found to significantly decrease spleen weight and the PFC response while equivalent doses of chrysene did not. Silkworth et al. (1995) reported that of 15 PAHs tested, chrysene was the most potent immunosuppressant in both male C57Bl6J and B6.D2 mice, resulting in suppression of the PFC (Plaque forming cell) response at doses as low as 0.05 mg/kg (0.219 µmol/kg) following a single oral dose. Subjects were also monitored for formation of globin adducts of chrysene. In both these cases, the procedure involved measurement of the respective PAH tetrols released from globin by acid hydrolysis. Levels of BPDE (benzo-[a]pyrenediolepoxide) adducts in the smokers were 2.7-fold higher than in the non-smokers (P<0.01), and although the chrysene diol-epoxide adducts were 25% higher in smokers, this was not statistically significant (P= 0.06) (Melikian et al. 1997).

Chrysene is on the right to know Hazardous Substances List because it is cited by OSHA, ACGIH, DOT, NIOSH, DEP, IARC, IRIS and EPA. Some of these agencies have also prescribed the workplace exposure limits of chrysene as well (Table 2).

- OSHA- Occupational Safety and Health Administration
- ACGIH- American Conference of Governmental Industrial Hygienists
- DOT- Department of Transportation
- NIOSH- National Institute for Occupational Safety and Health
- DEP- New Jersey Department of Environmental Protection
- IARC- International Agency for Research on Cancer
- IRIS- Integrated Risk Information System Database
- EPA- Environmental Protection Agency

Table 2 Workplace Exposure limit of Chrysene

	Workplace Exposure Limit of Chrysene
OSHA	The legal airborne permissible limit (PEL) is 0.2 mg/m^3 (as coal tar pitch volatile, benzene-soluble fraction) average over an 8 hour work shift
NIOSH	The recommended airborne exposure limit (REL) is 0.1 mg/m^3 (as coal tar pitch volatiles, cyclohexane-extractable fraction) average over a 10 hour work shift
ACGIH	Recommends that exposure by all routes to be controlled to levels as low as low possible

VARIOUS CARCINOGENIC ISOFORMS OF CHRYSENE

5-Methylchrysene

The complex reactions during the combustion process lead to the formation of unsubstituted (parent) as well as methylated PAHs (Badger et al.1952). As a result, mixtures of parent and methylated PAHs are found in the environment (Blumer and Youngblood, 1975; West et al.1986). Structural features have been reported to be the key factor in determining the potency of a PAH as a carcinogen. It has been observed that substituted PAHs with greater steric hindrance are more tumorigenic than their less hindered counterparts, having the same number of rings. For example, 7, 12-dimethylbenz[a]anthracene, 5-methylchrysene (5-MeC) (Fig. 1), and 11-methylbenzo[a]pyrene, having a methyl group in the bay region, are more carcinogenic than their respective parent PAHs (Huggins et al. 1967; DiGiovanni et al. 1983; Hecht et al.1987; Iyer et al. 1980).

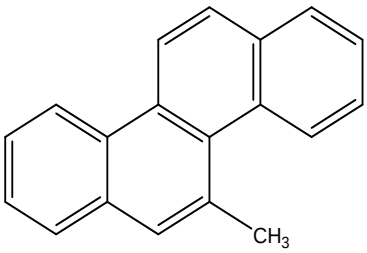

Figure 1 Chemical structure of 5-Methylchrysene

Dihydrodiols and diol epoxides are implicated as the active forms of carcinogenic polynuclear aromatic hydrocarbons (PAHs) (Wislocki and Lu, 1988; Lehr et al. 1985 and Dipple et al. 1994). These electrophilic metabolites interact covalently with cellular DNA, leading initially to mutation, and ultimately to tumor induction (Dipple et al. 1994). Methyl substitution in the bay-region of PAHs often results in significantly more potent carcinogens. For example, the substitution of weakly carcinogenic chrysene at the bay-region position 5 resulted in the potent carcinogen 5-methylchrysene, whereas the substitution of the methyl group at any other position of chrysene produced monomethylchrysenes with carcinogenic potencies far less than that of 5-methylchrysene.

Alkyl-substituted PAHs are considered to be more persistent in the environment than their unsubstituted analogs (Gundlack et al. 1983). Also, the methylated PAHs are often more carcinogenic than the parent hydrocarbons and their carcinogenic activity varies with the position of the methyl substituent in the aromatic nucleus (Hecht et al. 1988; Yang, 1988). Methyl substitution in a non-benzo ring, bay-region position generally enhances the carcinogenicity of PAHs (DiGiovanni et al.1983; Hecht et al. 1986; LaVoie et al.1981). The carcinogenic effects of the methylated PAHs are due to the metabolic conversion of the parent hydrocarbon to specific electrophilic metabolites, which readily react with cellular macromolecules, including DNA resulting in adverse consequences (Hecht et al. 1988). Therefore, it is important to investigate the metabolism of these chemicals in aquatic organisms in order to assess the mutagenic/ carcinogenic potential of methylated PAHs in these organisms.

6-Nitrochrysene

Ubiquitous environmental agents that are known to induce mammary cancer in rodents must be regarded as potential human risk factors and need to be evaluated more closely. An example of such environmental carcinogens is the class of nitropoly-nuclear aromatic hydrocarbons (NO_2-PAHs) (El-Bayoumy et al. 1994; Fu and Herreno-Saenz, 1999; Tokiwa et al. 1993). 6-nitrochrysene (6-NC) (Fig. 2) is a representative example of this class of carcinogens. The significant carcinogenic activity of 6-NC in the rat mammary gland, its environmental occurrence, the ability of human liver, lung and breast tissue to convert 6-NC into DNA-reactive metabolites, as well as the finding of its hemoglobin adducts in humans suggest that it probably contributes to the development of human breast cancer (IARC 1989; El-Bayoumy et al.1993; Chae et al.1993; Boyiri et al. 2002; Zwirner-Baier and Neumann, 1999).

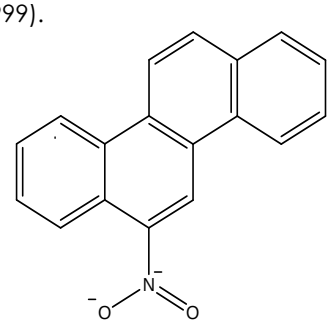

Figure 2 Chemical structure of 6-nitrochrysene

In fact, several studies reported on the detection of DNA adducts in human breast tissue; however, the nature of these adducts remains unknown (Seidman et al. 1988; Perera et al. 1995; Li et al. 1996; Pfau et al.1998; Wang et al.1996).

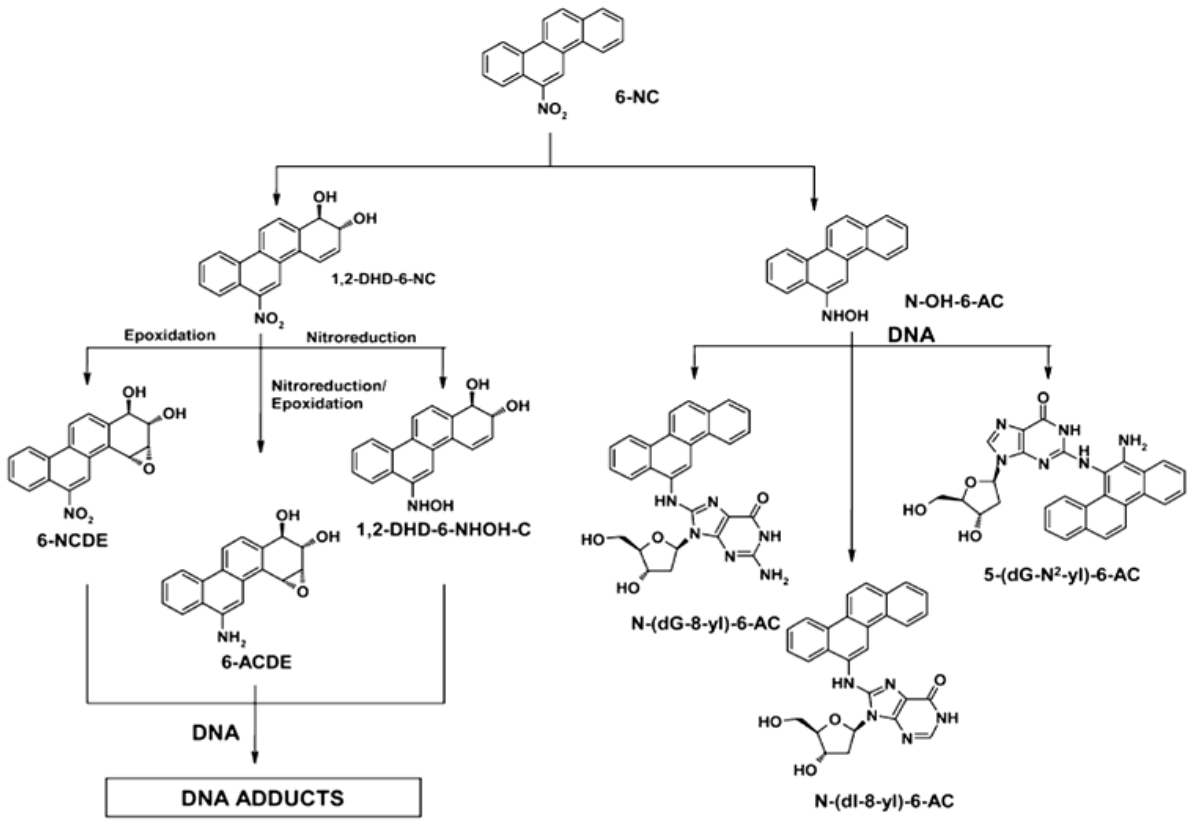

Figure 3 Proposed metabolic activation pathways of 6-NC. Adducts derived from nitro-reduction of 6-NC are: *N*-(deoxyguanosin- 8-yl)-6-aminochrysene; 5-(deoxyguanosin-N^2-yl)-6-aminochrysene; *N*-(deoxyinosin-8-yl)-6-amino-chrysene. Adducts derived from 6-NCDE and from 1, 2-DHD-*N*-OH-6-AC have not been characterized (Karam et al. 2004)

Figure 3 depicts that 6-NC can be activated by two pathways. The first pathway proceeds via simple nitro-reduction to form N-hydroxy-6- aminochrysene (N-OH-6-AC) that yields three DNA adducts; the structures of these adducts have been characterized (Chae et al. 1996) . The second pathway involves a combination of nitro-reduction and ring-oxidation yielding a very reactive electrophile, trans-1, 2-dihydroxy- 1,2-dihydro-N-hydroxy-6-aminochrysene, that primarily leads to the formation of a major adduct, yet to be structurally characterized.

Dibenzo[*c*,*p*]chrysene (DB[*c*,*p*]C)

There is another isoform of chrysene, DBC (Fig. 4) that has been observed to be a highly potent carcinogen in studies in laboratory animals (Cavalieri et al. 1989; Cavalieri et al. 1991; Higginbotham et al. 1993; Lavoie et al.1993; Prahalad et al.1997). DBC exposure has been shown to cause skin tumors in SENCAR mice exposed dermally (Cavalieri et al.1989; Cavalieri et al.1991; Higginbotham et al. 1993; Lavoie et al. 1993), mammary tumors in Sprague Dawley rats exposed intramammarily (Cavalieri et al. 1991), and lung and liver cancers in CD-1 and A/J mice exposed intrapertioneally (Prahalad et al. 1997; Platt et al. 2004). DBC has been found to be approximately 100-fold more potent in producing lung adenomas than B[a]P (Prahalad et al. 1997). Recently, DBC has been shown to cross the placenta in B6129SF1/J mice, causing T-cell lymphoma, lung adenoma, and liver lesions in offspring of mothers exposed to single doses of 15 mg/kg DBC (Yu et al. 2006; Castro et al. 2008). The International Agency for Research on Cancer (IARC) currently classifies DBC as a 2B, or possibly carcinogenic to humans (IARC, 2010).

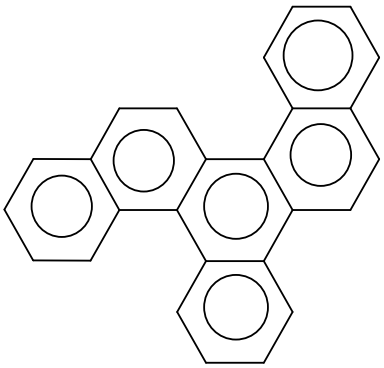

Figure 4 Structure of Dibenzo[*c*,*p*]chrysene (DB[*c*,*p*]C)

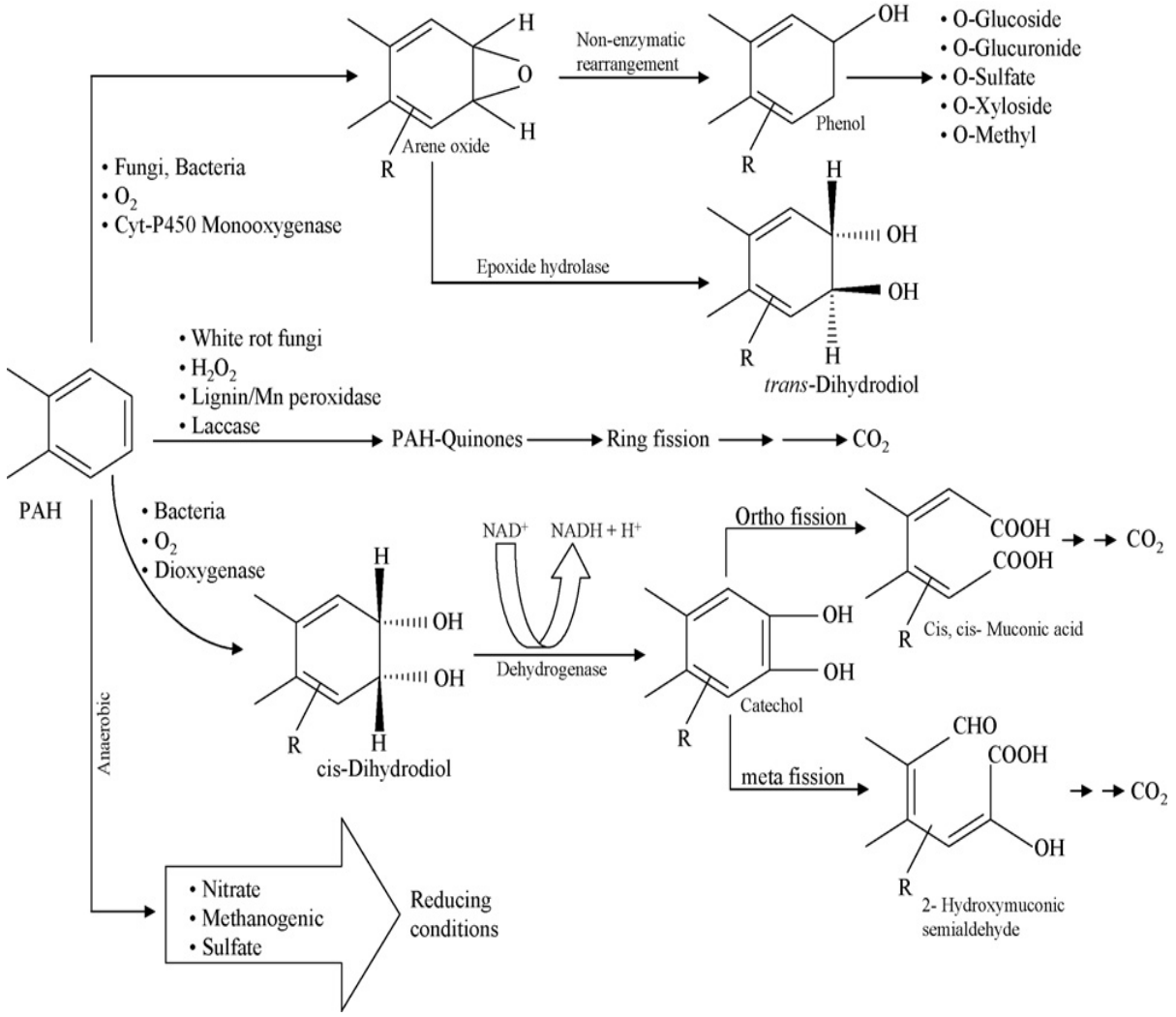

Figure 5 Proposed pathway for microbial catabolism of polycyclic aromatic hydrocarbons (Cerniglia, 1992)

Discussion

Chrysene and its different isoforms are proven carcinogens. Humans and other life forms are exposed to them from a variety of sources. Ever since the industrial revolution begins in 18th century, environmental contamination by human activities and other sources remains a continuous problem for the mankind. PAHs are hazardous environmental pollutants that can have a detrimental effect on the flora and fauna of the affected habitats, resulting in the uptake and accumulation of these toxic chemicals in food chains. Such trophic level transfer of toxic pollutants in food chains may results in serious health problems and/or genetic defects in humans. High molecular weight PAHs contain a 'bay-region' as well as 'K-region', both of which allow metabolic formation of bay- and K-region epoxides, which are highly reactive. Carcinogenicity has been demonstrated by some of these epoxides (Goldman, 2001). Very little information is available on the metabolic pathway of high molecular weight PAHs but the overall route of pathway is known (Fig. 5). It is now understood that the initial step in the aerobic catabolism of a PAH molecule by bacteria occurs via oxidation of the PAH to a dihydrodiol by a multi-component enzyme system. These dihydroxylated intermediates may then be processed through either an *ortho*-cleavage type of pathway or a *meta*-cleavage type of pathway, leading to central intermediates such as protocatechuates and catechols, that are further converted to tri-carboxylic acid cycle intermediates (Van der et al. 1992).

CONCLUSION

PAHs including chrysene are ubiquitous environmental pollutants. PAHs are processed by dioxygenase enzymes in living system and results in reactive epoxides which are highly toxic, carcinogenic and mutagenic to humans and other life forms including microbes than their parent compound. They are found to cause different type of cancers in laboratory animals when

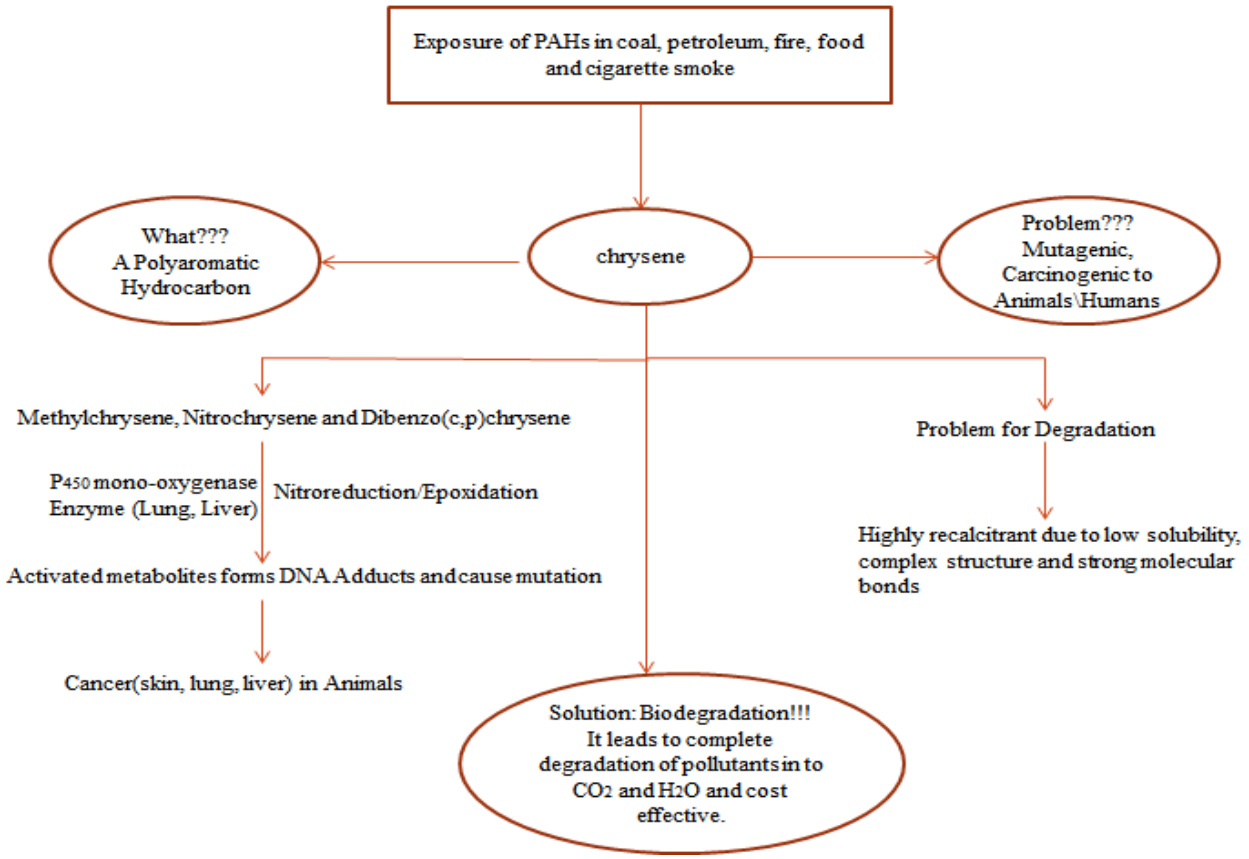

Figure 6 Shows the route of exposure, toxicity and remediation of High molecular weight PAH Chrysene

exposed to them at different concentrations. That is why their fate in the environment is of great concern. Humans and other life forms are exposed to them from a variety of sources. Low molecular weight PAHs those having two or three aromatic rings can be degraded favorably by the soil microbes but those with high molecular weight composed of four or five aromatic rings are recalcitrant. Bioremediation can be used as a promising technology for the removal of such compounds from the environment in a cost effective manner. Soil microbes naturally possess ability to degrade a variety of PAHs and till to date variety of microbes and fungi are isolated that are capable of utilizing PAHs and convert them to non-toxic form. PAHs degrading micro-organism have potential for bioremediation but there is requirement for certain modifications to make such micro-organisms effective and efficient in removing the recalcitrant organic compounds. There are certain factors like pH, temperature, nutrient availability and surfactants which reduces the efficiency of bioremediation by microbes. Hence the complete protocol of PAHs could only emerge if more research and efforts are directed to study their interaction in the process of bioremediation.

The biological treatment of soils contaminated with PAH should be an efficient, economic and versatile alternative to physio-chemical treatment because it offers potential advantage for the complete degradeation of organic pollutants, comparatively at low treatment cost, and greater safety and also offers less environmental disturbance. Therefore researchers need to focus on the bioremediation aspect of PAHs and to look forward for innovative biotechnological strategies to remove such hazardous pollutants from the environment. A flow diagram for justification of bioremediation of chrysene is given in figure 6.

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