Toxicity, Mutagenicity and carcinogenicity of phenols and phenolic compounds on human and living organisms [A Review]

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INTRODUCTION

Phenols and phenolic compounds are of environmental concern due to their toxicity and being as ubiquitous contaminants in the environment.

The presence of phenolic compounds in soils is due to different sources including industrial activities of chemical, textile, pharmaceutical, polymers, pulp and paper, woods, plasticizers, pesticide, and metallurgic industries or by the release of industrial effluents and domestic sewage [1-3]. Some phenols in the soils originate from the transformation of pesticides such as 2,4-dichlorophenoxyacetic acid (2,4-D), 4-chloro-2-methylphenoxyacetic acid (MCPA), 2,4,5-trichloro-phenoxyacetic acid (2,4,5-T), 2-buthyl-4,6-dinitrophenol (dinosb), and phenolic biocides like pentachlorophenol (PCP)[4] and from atmospheric depositions [5]. Moreover, nitrophenols and methylphenol sources have been related to vehicular emissions [6,7] Phenols may occur naturally via biodegradation of humic products, for example tannins and lignins[8]. Some phenols may be formed as a result of natural processes like the formation of phenol and p-cresol during decomposition of organic matter or synthesis of chlorinated phenols by fungi and plants [9].

Effects on Experimental animals:
Systemic effects:

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Only experimental oral studies are available; the chronic toxicity of PCP by the oral route is very well documented. In rodents, biochemical, functional and histopathological changes in the liver have been widely described for daily doses of 1–30 mg/kg over periods of 3–8 months [10,11]. Evidence of biochemical (alterations in hepatic enzyme activities), gross (increased liver weight) and histopathological (hypertrophy, vacuolization, hyperplasia, fibrosis, necrosis and degeneration) effects is found following acute, intermediate and chronic oral exposure to PCP in rodents. At low dosages, the observed liver effects are characteristic of enzyme induction. Increase in liver weight and hepatocellular hypertrophy and vacuolization have been observed in mice exposed to pure PCP at 41 mg/kg bw per day for 2 weeks [12], in rats exposed to pure or technical grade PCP at 1–40 mg/kg bw per day for an intermediate duration [13–16,11], in mice exposed to pure or technical-grade PCP at 9 mg/kg bw per day for 4–12 weeks [17,12] and pigs exposed to pure PCP at 10 mg/kg bw per day for 30 days [18].

Purified PCP (2 mg/kg bw per day, only dose tested, >99% pure with no detectable chlorinated dibenzo-p-dioxin impurities) also induced a small but significant increase in relative liver weight in rats exposed twice weekly for 28 days.

Histological examination was not performed [14]. The National Toxicology Program [19,20] conducted a 28-day dietary range-finding study with pure PCP (20–270 mg/kg bw per day, approximately 99% pure, containing tetrachlorophenol as a single impurity) in F344 rats.

Significantly increased absolute or relative liver weights were seen at all dose levels.

Hepatocyte degeneration and centrilobular hypertrophy were seen at 40 mg/kg bw per day and higher in males, and at 75 mg/kg bw per day and higher in females.

The results of the study by Kimbourgh & Linder [12] suggest that impurities found in technical grade PCP may influence its toxicity, but other studies that compared the hepatotoxicity of pure and technical grade PCP did not find differences in potency or type of liver effects [17,21].

Significant alterations in thyroid hormone levels have been observed in several chronic and intermediate-duration animal studies. A significant decrease in mean serum concentration of thyroxine and a significant increase in the mean serum concentration of insulin, compared with controls, was observed in female sheep administered PCP at 2 mg/kg bw per day (only dose tested; 99.9% pure) by gavage twice weekly for 43 days. Mean serum concentrations were based on blood samples taken every hour for 6 hours after 36 days of PCP treatment [22].

These results are confirmed on ewes and male lambs by Beard et al. [23,24]. In a multigeneration study in mink, significant decreases in serum thyroxine levels were observed in the F1 males and the F2 males and females exposed to PCP at 1 mg/kg bw per day (purity not reported) [25]. A decrease in relative thyroid weight was also observed in the F2 female mink.

A study of mice exposed in parallel to two preparations of PCP at 25 mg/kg bw per day for 10–12 weeks concluded that the impurities play an essential but non-exclusive role in immune system malfunctions [17], mainly deterioration of the T-cells. However, a study in rats provides evidence that pure PCP can affect immune function [14].

The haematological effects appear to be due largely to the impurities present in industrial preparations of PCP [10]. Nevertheless, a fall in the white blood cell count has been described in pigs following administration of purified PCP [18].

Hypothermia resulting from the decoupling of the oxidizing phosphorylation process is probably the reason for the neurological effects observed in animals. In rats, the administration of PCP in drinking-water (purity not specified) led after 14 weeks to a reduction of the glutathion level in nerve tissue, which is responsible for activating a number of enzymes [26]. Again in rats, de-myelination of the sciatic nerve was observed after administration of PCP (1 and 3 mM) in drinking-water for three months.

Acute Toxicity:

Phenol irritates skin and causes its necrosis, it damages kidneys, liver, muscle and eyes. Damage to skin is caused by its coagulation related to reaction to phenol with amino acids contained in keratin of epidermis and collagen in inner skin [27]. In a dose of 1 g phenol may be lethal for an adult man, but individual tolerance for this compound can be high. Some reports reveal that a man can survive even after administration of 30 g of this compound in regard to fast absorption by skin even contact of hand or forehead with phenol solution may cause death [28].

Acute poison with phenol is characterized by dryness in throat and mouth, dark-coloured urine and strong irritation of mucous membranes. The investigations showed that chronic administration of phenol by animals leads to pathological changes in skin, esophagus, lungs, liver, kidneys and also urogenital tract. Described changes are mainly induced by lipid peroxidation that is responsible for damage and finally degradation of a cell’s membrane.

Chronic exposure of workers to phenol vapours causes anorexia, lost of body weight, weakness, headache, muscles pain and icterus [29]. Phenol is mainly accumulated in brain, kidneys, liver and muscles. Two days
after phenol administration it is mainly excreted in unchanged form and also conjugated with sulphates and glucuronides. catechol is also considered a strong toxin. Doses of 50 to 500 mg/kg of body weight usually cause death. For mice after oral administration of catechol LD50 is 260 mg/kg of body weight.

Acute poison with chlorophenols is characterized by burning pain in mouth and throat, white necrotic lesions in mouth, esophagus and stomach, vomiting, headache, irregular pulse, decrease of temperature and muscle weakness, convulsions and death [30]. Chronic exposure to chlorophenols cause hypotension, fall of body temperature, weakness and abdominal pain. Poisoning by chlorophenols results in damage to lungs, liver, kidneys, skin and digestive tract. Strong toxicity of chlorophenols is expressed by very low, acceptable daily intake (ADI) for pentachlorophenol that was established for 16 µg for a man of 70 kg of bodyweight. ID50 for male and female of rats after oral administration of PCP is 14 mg and 3.85 mg/kg of bodyweight respectively [31]. For 2,4,5-trichlorophenol LD50 is much higher and is of 820 mg/kg of body weight. Air pollution with a mixture that contained 2-chloro-6-fluorophenol is the result of an accident in a chemical factory (New York, USA) that caused symptoms like dryness in mouth and throat, coughs, headaches and abdominal pain [32]. Chlorophenols undergo fast absorption by skin and mucous membrane of respiratory system.

Pentachlorophenol and tetrachlorophenol dissolved in fats are adsorbed by skin in 62% and 63% respectively. chlorophenol accumulation proceeds in kidneys, spleen, liver, heart, brain and fat tissue. Clinical symptoms related to poisons with nitrophenols are similar to that exerted by chlorophenols. 2,4-di-nitrophenol has been used as a slimming drug and as an additive in food at the beginning of the last century. Numerous cases of chronic heat, depression and deaths led to this compound being removed from the market [33].

It is considered that a lethal dose of 2,4-dinitrophenol for a man is of 14 to 35 mg/kg of bodyweight [34]. Lethal doses (ID50) of nitrophenol orally administered to rats and mice are 450-850 mg/kg and 380 mg/kg of body weight, respectively, and for dinitrophenol (rats) only 30 mg/kg of bodyweight [35]. 2,4-dinitrophenol undergoes fast absorption by skin and respiratory system, it is also quickly absorbed from the digestive tract. The compound is accumulated in blood plasma, kidneys, lungs and liver [36]. In work, acute poison as the result of one intake of 2,4-dinitrophenol has been described. In the first hour after poisoning a high increase of temperature and intense perspiration was observed. In the next hour, in spite of antidotes being applied, contact with the patient was broken and circulatory and cardiac failure caused death.

The highest occupational exposure is noted form methylphenols. It has been estimated that in world exposure to 4-methylphenol concerns some 600 to 1,200 thousands of workers. This mainly refers to workers who produce antioxidants, disinfectants, dyes, plastics, explosives, epoxy-resins, coal tar and steel [37]. Acute poison with methylphenols cause burning pain in mouth and throat, abdominal pain, headache, weak irregular pulse, hypotension, fall of body temperature, stentorous breathing, dark-colored urine, shock, paralysis of nervous system, coma and death. The incident of poison related with intentional administration of 140 ml of 50% of 4-methylphenol solution by a man has led to an increase of plasma aminotransferases activity and then degradation of hepatocytes. In spite of intensive detoxification, the sufferer died after 14 days [38]. It is considered that a lethal dose of 4-methylphenol for man is of 30-60 g [39]. Lethal doses for animals are different in regards to the type of chemical structure of methylphenols. For example, ID50 for rats that were orally administrated of 2,4-dimethylphenol was estimated for 207 mg/kg of body weight [40].

Para-cresol is absorbed by skin, mucous membrane of digestive tract and respiratory system. It is excreted in urine and in a low concentration with bile and expired air [29]. 30 minutes after administration, 2,4-dimethylphenol is metabolized and excreted 94% conjugated with glucuronides and other conjugates. Considerable toxicity exerts 4-aminophenol. This compound causes skin and eye irritation, eczemas, asthma and anoxia [29].

Aminophenol toxicity is related with generation of semiquinones and superoxide radicals that damage a cell’s biomolecules. P-aminophenol by formation quinonimines damages cell membranes and in particular (in doses of 200 mg/kg of body weight) is characterized by nephotoxic influence [41]. Lethal doses of p-aminophenol for man are estimated at 50 to 500 mg/kg of body weight. ID50 for rat after oral administration is much higher and is of 1580 mg/kg of body weight.

The investigations revealed that butylhydroxytoluene and butylhydroxyanisole reveal histopathological activity. Those compounds cause damage of adrenal gland and increase brain and liver weight [42]. The results of clinical investigation also describe mass poison with chlorophenols. The example is pollution of water and fish in reservoir in Jarrela locality in south Finland with a mixture of 2,4,6-trichlorophenol, 2,3,4,6-tetrachlorophenol and pentachlorophenol derived from a wood processing plant. As the result of poison of about 2000 people—the consummates of water and fish increase morbidity on the side of digestive tract. Also, the increase of infections of respiratory system, strong exhaustion, headaches and depression were observed [43].

**Nervous system toxicity:**

Phenols also modulate the activity of ion channels in the nervous system. It was noted that simple phenols and in particular trichlorophenols, trijodophenols and butylphenol may block ion channels in a micromolar
concentrations range. The conclusion of investigation was that phenol and hydrophobic residues – alkyl chains or additional phenyl rings substituted in third, fourth and fifth positions are responsible for the above-described kind of toxic activity [44].

**Digestive system toxicity:**

Some phenols like phenol and P-cresole may be formed from non-toxic compounds like tyrosine in digestive tract of mammals, including humans. P-cresol is also a marker of organism exposure to toluene. This compound in the presence of hydrogen peroxide caused DNA adducts formation in hl-60 cells. Researchers revealed that DNA damages were induced by a metabolite of 4-methylphenol – quinonemethide of p-cresol (PcQm) that also may be used as biomarker of organism exposure to toluene influence [45]. Damages caused by aminophenols are related to fast oxidation of these compounds in physiological conditions to benzoquinonoidines that are finally transformed to p-benzoquinonoidines. The second metabolite generates a superoxide radical that in a dismutation reaction forms hydrogen peroxide converted in the presence of Fe3+ to a highly reactive oxygen form – hydroxyl radical. In an experiment damage of epithelium cells of colon was induced by catechol and p-aminophenol. As the authors suggest, the above process may lead to chronic inflammation of large intestine [46].

The investigations led by Bukowska, Duchnowicz and co-workers have revealed numerous toxic effects caused by phenols on human erythrocytes. The authors observed lipid peroxidation in erythrocytes incubated with 2,4-di-chlorophenol, 2,4,5-trichlorophenol, 2,4-dimethylphenol, and 3-(dimethylamino)-phenol [47-50]. chlorophenols and catechol decreased human membrane erythrocytes acetylcholinesterase activity [51] chlorophenol and dimethylphenol changed ATPase activity and membrane fluidity and also damaged membrane proteins [47-51]. All investigated phenols oxidized haemoglobin, and the highest activity was revealed by 3-(dimethylamino)-phenol, catechol and 2,4-dimethylphenol (2,4-DmP) [47-52]. 2,4-dichlorophenol (2,4-DCP), 2,4,5-trichlorophenol (2,4,5-TcP) and catechol decreased the activity of catalase [53]. Moreover, catechol decreased superoxide dismutase activity [54]. in the presence of 2,4-DmP and 2,4,5-TcP, a decrease in the amount of ATP that coincided with a simultaneous increase in ADP and AMP content was observed, which in the consequence caused a decrease of the energy charge of erythrocytes [55]. The changes in the above parameters provoked haemolysis of the cells. The level of haemolysis was the highest in the presence of catechol and the lowest in the presence of phenol. In the light of obtained results the most toxic compounds towards erythrocytes were 3-(dimethylamino)-phenol and catechol.

**Immunotoxicity:**

Other toxic influence of Phenols 4-octylphenol and 4-nonylphenol induce immuno-toxicity by inhibition of lymphocytes proliferation. The second compound revealed stronger toxic activity and induced this process even in a concentration of 1 µm/kg of body weight [56]. Administration of 4-nonylphenol to rats in doses of 125-375 mg/kg of body weight caused changes in the activity of the immunological system. The mechanism of action was related to modulation of genes expression that are responsible for mRNA synthesis in thymocytes. Decrease of mRNA synthesis led to apoptosis and finally inhibited thymocyte proliferation [57].

**Reproductive system toxicity:**

Phenols also affect the function of the hormonal system. Some phenols are capable of disturbing sexual hormones function, which finally may lead to sterility of animals and humans. The examples are alkylphenols, bisphenol A, 2, 4-dichlorophenol and pentachlorophenol [58,59]. Those compounds express their activity by binding with ER receptors. There are some places within a receptor that may bind not only 17β-hydroxyl groups of hormones but also hydroxyl residues of phenols as well. Moreover, it is considered that core of alkylphenols imitates a ring A in E2 estrogens and thus reveal estrogenic activity [60]. In another experiment bisphenol A caused protein expressions in Tm4 cells in mice, which play a key role in spermatogenesis. It was noted that viability of cells decreased 10 to 70% after exposure to doses of 50-250 µm/kg of body weight over 16 hours, obtained results showed that bisphenol A may induce infertility in mice.

Only experimental oral studies are available. Numerous data suggest that long-term exposure to PCP can decrease fertility, although the mechanism does not appear to be through histological damage to reproductive tissue. In a two-generation study, decreased fertility (significant decreases in the number of rats mated and in the ratio of pregnant rats to the number of rats in cohabitation) was observed in the first generation of rats exposed to 60 mg/kg bw per day PCP (purity not reported) administered by gavage [61]. No alterations in fertility were observed in the F1 generation exposed to 10 or 30 mg/kg bw per day or in the parent generation. The only other reproductive effects observed in this study were a significant decrease in testicular spermadit count, a decrease in absolute testes weight and in the ratio of testes weight to brain weight, and focal/multifocal mononuclear cell infiltrate in the epididymis in F1 rats administered 30 or 60 mg/kg bw per day. Other alterations were observed on the F1 generation in different studies where minks were exposed to 1 mg/kg bw per day PCP (purity not
reported) in the diet for 3 weeks prior to mating [25,62]. The effects were not found in sheep exposed before mating[63, 24].

Several reproductive toxicity studies have reported histological alterations in reproductive tissues. Beard et al.[23] reported focal degeneration of the seminiferous tubules and decreased sperm density in the epididymis in sheep exposed to PCP (purity not re-reported) at 1 mg/kg per day in the diet during gestation, lactation and for 20 weeks postnatally. Chhabra et al.[19] and NTP [17] reported minimal to marked germinal degeneration and lack of spermatooza in the seminiferous tubules of rats exposed to pure PCP at 270 mg/kg per day in the diet for 28 days. Beard et al.[62] reported increased severity of cystic uterine glands in mink exposed to PCP at 1 mg/kg per day prior to mating and during gestation and lactation. No histological alterations in reproductive tissues were observed in male or female rats chronically exposed to pure PCP at 30 mg/kg per day in the diet for 2 years [19,16].

The toxicity of PCP to rat embryos and fetuses has been confirmed in other studies [13, 64,65,66]. In another study, Bernard & Hoberman [13]. exposed Sprague Dawley rats by gavage to PCP at 0, 10, 30 and 80 mg/kg/day in corn oil from day 6–15 of presumed gestation. From this study they determined a NOAEL of 30 mg/kg/day for maternal toxicity in Sprague Dawley rats. A developmental NOAEL for PCP was also found to be 30 mg/kg/day and the LOAEL for PCP developmental toxicity of 80 mg/kg/day was associated with increased resorptions and reduced live litter size and fetal body weights, and caused increased malformations and variations. The authors concluded that PCP should not be identified as a selective developmental toxicant in the rat because adverse effects on development of rat conceptuses occurred only at dosages toxic to the mother. In hamsters, oral administration of PCP at doses between 1.25 and 20 mg/kg resulted in fetal death in a number of groups [67].

No developmental effects were observed in rabbits administered 88–89% pure PCP at up to 30 mg/kg/day by gavage on gestational days 6–18 [64].

**Mutagenicity:**

The investigations of hamster fibroblasts revealed mutagenic activity of phenol. This compound also inhibited synthesis and replication of DNA in helic cells [68]. In another experiment phenol stopped reparation of DNA in diploid human fibroblasts. Hydroquinone (1,4-dihydroxyphenol) induced damages of chromosomes in human lymphocytes, increasing deletion ratio in 7. chromosome, which may lead to leukemia development [69]. In another experiment phenol, catechol and hydroquinone induced morphological changes in cells of hamster embryos. In another experiment catechol and hydroquinone inhibited ribonucleotidereductase activity (the enzyme that participates in DNA synthesis) and thus stopped activation and proliferation of T lymphocytes. Those compounds also inhibited the proliferation cycle of lymphocytes in g1 phase[70]. Catechol in the presence of NADPh and Cu2+ was able to modify guanine and tymine residues and induce gene mutations and chromosome aberrations. Catechol and hydroquinone damaged chromatides and induced incorrect DNA synthesis. The similar changes were provoked by pyrogallol, which induced the strongest (among hydroxybenzenes) chromosome aberrations. Pyrogallol and hydroquinone expressed their toxicity by forming a reactive oxygen species that included a hydroxy radical that caused deprotonation of the substrates and thus degraded deoxyxybose[71]. It was also observed that semiquinone and quinone radicals are involved in damage of DNA structure by discussed xenobiotics. chromosome aberrations and other structural changes within chromosomes were also induced by pentachlorophenol and proceeded even at low concentrations of PcpP[72]. Damage of DNA was provoked by the formation of the PCP product – tetrachlorohydroquinone and also harmful intermediate form – tetrachloroquinone radical (TcsQ) that degraded DNA and handicapped the mechanisms responsible for its repair [73].

Mutagenic influence was also exerted by nitrophenols and nitrated aminophenols. In the test with the use of Salmonella typhimurium mutagenic activity was observed for 2,3-dinitrophenol, 2,5-dinitrophenol, 3,4-dinitrophenol, 2,4,6-trinitrophenol and 2-nitro-5-aminophenol. In another experiment performed on Salmonella typhimurium and Escherichia coli, mutagenic activity was noted for bisphenol F. This compound induced the increase of frequency of sister chromatide exchange and decreased the number of micronucleus in human lymphocytes [74].

4-aminophenol is capable of interacting with genetic material at the presence of Fe3+ and thus damages DNA contained in mouse and human lymphocytes. The process was related with action of free radicals that were formed in the reaction of iron ions and hydrogen peroxide [75] some bhA and bhT metabolites also reveal genotoxic capacity toward DNA. Tert-butylhydroquinone (TbhQ) is formed in cells from butythlyhydroxyanisole in oxidative demethylation reaction and reveals genotoxic, cytotoxic, clastogenic and mutagenic capacities. 2,5-di-tert-buthylhydroquinone (DTbhQ) is formed from 2,5-di-tert-buthylhydroxyanisole (DTbhA), the compound that contaminates commercial preparations of bhA. In performed experiment both DTbhQ and DTbhA unplaited DNA helix by cleavage of single and double hydrogen bonds.

TbhQ revealed stronger activity – 92.5% of DNA structure was damaged. As free radical scavengers like glutathione were activated in this process, it was considered
that DNA cleavage was induced by free radicals generated by describing metabolites [76]. bhT metabolism is related with hydroxylation of alkyl substituents, and also with oxidation of aromatic ring. in the experiment some butylyhydroxianisole metabolites like 2,6-diterbutyl-4-hydroxy-4-methyl-2 cyclohexadienone (bhT-ooh) and 2,6-diterbutyl-4-benzoquinone (bhT-quinone) caused damage to DNA in the presence of Cu2+ by cleavage of hydrogen bounds. These compounds also induced characteristics of apoptosis endonucleosomal DNA fragmentation. The mechanism of action of both metabolites was different: bhT-oohin directly damaged genetic material and bhT-quinone interacted by the formation of hydrogen peroxide [77].

Carcinogenicity:
Clinical data have shown that people exposed to chlorophenols influence fall ill with of tumours, sarcoma and lung cancer. According to literature data the mixture of chlorophenols or sodium salts of these compounds is probably carcinogenic for animals [78]. An admissible daily dose of individual chlorophenol that may be taken by a man that does not induce carcinogenic changes is 5µg/kg of body weight for 2-chlorophenol, and 3µg/kg of body weight for 2,4-dichlorophenol, 2,4,6-trichlorophenol and pentachlorophenol [79]. catechol also reveals carcinogenic activity.

Paracresol was classified as probable carcinogenic for human [80] and 2,4-dimethylphenol was considered as the compound responsible for carcinogenic influence [81]. chronic exposure of skin rats to 2,4-dimethylphenol caused the formation of skin tumours (31% towards control). in the experiment an additional application of 3% dimethyl-benzanthracene caused the formation of skin tumours (50% towards control) and 18% of skin cancer. These changes were induced by o-quinones, in particular quinonesmethide that revealed high toxicity and additionally generated reactive oxygen species [82]. Occupational exposure of workers to phenoxyherbicides is related to an increase of death incidents. The observed increase of mortality was linked to morbidity on cancer of respiratory system, lymphoma and myocardial ischaemia [83]. The positive correlation was also noted between non-hodgekins lymphoma appearance among children and documented frequency of using pesticides and their effect on the organism of birth child [84]. The investigations of 10,000 workers employed in vinyl chloride production factories revealed that they suffered from liver and lung cancer [85]. chlorophenols are the main byproducts that are formed during vinyl chloride production. The exposure of people to chlorophenol influence appears also in factories that produce chloroorganic pesticides, mainly phenolic biocides. The main compound that is formed in this process is pentachlorophenol that was classified by the U.S. ePA as a probable carcinogen. The workers that are employed in pesticides production suffer from non-Hodgekins lymphoma and sarcoma [86]. carcinogenic properties are also characteristic for 4-methylcatechol and 4-methoxyphenol that are responsible for skin cancer and epithelium cancer development. in an experiment catechol, 4-methoxyphenol and butylyhydroxianisole individually and particularly in mixture induced papillomas in stomach of rats [87]. carcinogenic activities of catechol were also confirmed in investigations of mice, the compound given in a dose of 85 µg/kg of body weight in a few weeks caused skin cancer development. in other investigations 4-nonylphenol in concentrations of 25 and 250 ppm given in food to rats by 28 weeks provoked proliferation of cancer cells in lungs. in the experiment 8-hydroxy-2'-deoksuyanosine as a marker of DNA damage was determined [88].The cancer development in people exposed to phenols is related with microsomal activation of cytochrome P450.

The oxidation reactions lead to conversion of some xenobiotics to electrophilic forms that actively interact with a cell’s structures. For example, pentachlorophenol activation leads to the formation of tetrachloro-1,4-benzoqui-none and tetrachloro-1,2-benzoquinone by intermediate steps with formation of respective semiquinone radicals.

The IARC and USEPA classifications are based on a study on B6C3F1 mice of both sexes, in which oral administration at daily doses of 0, 100 and 200 ppm of two 90% pure preparations of PCP led to the development of a number of tumours, particularly in the males (adenomas and hepatocellular carcinomas, haemangiosarcomas and phaeochromocytomas) [89].

Many studies confirms these effects: groups of male and female F344 rats were given diets that contained 0, 200, 400 or 600 ppm PCP (approximately 99% pure with one impurity, tetrachlorophenol) in the diet (equivalent to doses of 0, 10, 20 or 30 mg/kg/day) for 105 weeks [16]. A stop-exposure group was given a diet that contained 1000 ppm PCP for 52 weeks (60 mg/kg/day) followed by a control diet through to 105 weeks. At 2 years, a significant increased incidence of malignant mesothelioma originating from the tunica vaginalis was present in males from the 60-mg/kg/day stop-exposure group compared with controls, and the incidence exceeded the historical control range. Nasal squamous cell carcinomas were present in one control male, three 10-mg/kg/day males, one 20-mg/kg/day male and five 60-mg/kg/day males at 2 years, and the incidence in 1000-ppm males exceeded the historical control range.

Toxicity in Fish:
Phenol and its derivatives induces toxic effect for fish. They induce genotoxic, carcinogenic, immunotoxic, hematological and physiological effects [90-94] and have a high bioaccumulation rate along the food chain due
to its lipophilicity. Thus phenol pollution represents a threat against natural environment and also to human health [95]. When phenol is present in the aquatic environment, fish food consumption, mean weight and fertility are significantly reduced [96].

Alteration in circulating levels of pollutants [97], leads to changes in the total lipids and cholesterol in fish. Genotoxic potency of metabolites was confirmed in derivatives inducing toxic effect for fish. They induce various fish species. Micronucleus test is one of the most genotoxic, carcinogenic, immunotoxic, hematological popular and promising test of environmental genotoxicity, and physiological effects [98-102] and have a high Micronuclei (MN) have been induced in fish exposed to bioaccumulation rate along the food chain due to its genotoxic substances like crude oil, petroleum refinery lipophilicity. Thus phenol pollution represents a great threat [103-105].

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