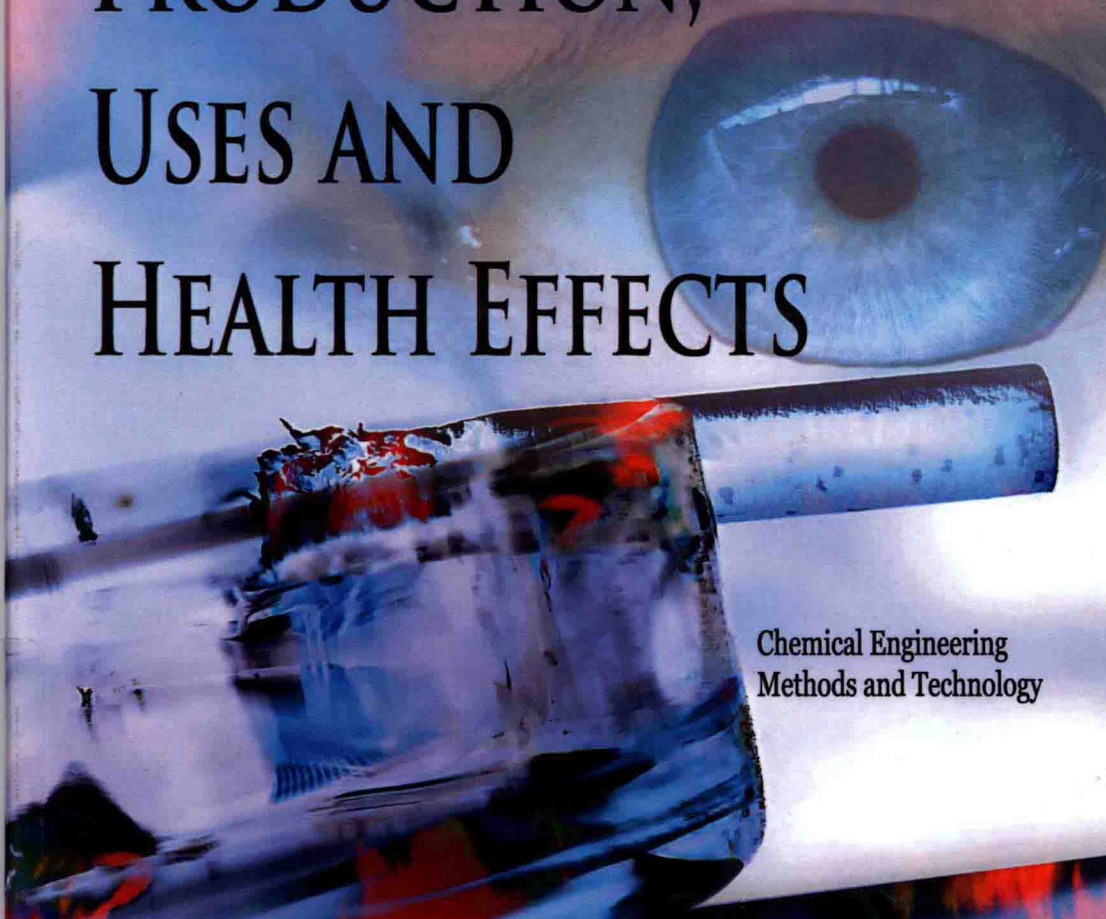
HYDROQUINONE

PRODUCTION, USES AND HEALTH EFFECTS



Chemical Engineering Methods and Technology

Fritz Gokden • André Lazzarotto
Editors

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AND
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PREFACE

Hydroquinone has a variety of uses principally associated with its action as a reducing agent which is soluble in water. It is a major component in most photographic developers for film and paper, and is used as a topical application in skin whitening to reduce the color of skin. In this book, the authors present current research in the production, uses and health effects of hydroquinone. Topics discussed include the cellular effects of hydroquinone; the involvement of cigarette smoke-related hydroquinone in the pathogenesis of age-related macular degeneration; hydroquinone solubility and separation processes; the transport and transfer processes of poly(o-aminophenol)film electrodes in the presence of the hydroquinone/p-benzoquinone redox couple and the detection of thiols using hydroquinone on gold surfaces.

Chapter 1 - The goal of this chapter is to review the most relevant scientific evidence supporting the role of cigarette smoke-related hydroquinone in the pathogenesis of age-related macular degeneration (AMD), a major cause of blindness among the elderly and to highlight the importance of smoking cessation to reduce the risk for developing AMD. AMD is a late onset (after age 50), progressive degeneration of the retina associated with vision loss coupled with a spectrum of specific clinical, physiological and histopathological features. The early or dry stage of AMD is characterized by the accumulation of drusen, specific lipid rich deposits under the retina whereas the late or wet stage is due to the growth of abnormal new vessels under the retinal pigment epithelium RPE) from the subjacent choroid, termed choroidal neovascularization (CNV). Extracellular matrix turnover (ECM], inflammation, and angiogenesis are key cellular processes that play a central role in the pathogenesis of AMD. The scientific evidences to support the interpretation of the RPE injury by hydroquinone are reviewed in depth,

especially the proposed role of hydroquinone on ECM turnover, inflammation, and CNV.

Chapter 2 - In chemical process design, separation unitsare usually very important for the purification of one or more components from the reaction stage. This step may involve different fluid or solid phases. Chemical engineering thermodynamics is the area of chemical engineering that studies the distribution of such components among equilibrium phases given temperature, pressure and feed composition. Therefore, reliable and accurate data on phase equilibria are crucial to optimize and scale up process separation units. As the number of real conditions in which the interest may be focused in is extremely high, thermodynamic models are frequently used to provide estimates of such data. Among these models, those based on the excess Gibbs energy, regularly known as activity coefficient models, and equations of stateare the most widely used. In this work, an overview of some thermodynamic models to describe the phase equilibria of hydroquinone and its isomers is provided, with the focus on the conditions commonly used for its separation processes. Results on the solid-liquid equilibria in water and organic solvents as a function of temperature, as well as in supercritical carbon dioxide as a function of pressure at several temperatures will be presented using the Non-Random Two Liquid Segment Activity Coefficient model (NRTL-SAC), the UNIFAC, the A-UNIFAC and the Cubic-plus-Association equation of state (CPA).

Chapter 3 - This review paper describes the different researches carried out in our laboratory to study transport and transfer processes at poly(*o*-aminophenol) (POAP) film electrodes in the presence of the hydroquinone/*p*-benzoquinone (HQ/Q) redox couple. The most significant experiments employing different techniques such as Cyclic Voltammetry, Rotating Disc Electrode Voltammetry and Electrochemical Impedance Spectroscopy are described in detail, and the application of existing models and theories that allow extracting charge-transport and charge-transfer parameters are also outlined. While an electron-transfer reaction (mediation reaction) occurs at negative potential values ($E < 0.0$ V *vs.* SCE), permeation processes are observed at positive potential values ($E > 0.8$ V *vs.* SCE). Freshly prepared poly(*o*-aminophenol) films were quantitatively deactivated to study how their permeation and charge-transfer processes are affected by the degree of deactivation (θ_c). While for low degrees of deactivation ($\theta_c < 0.4$) it is possible to recover the conductivity of a deactivated POAP film by reactivation in an alkaline solution, high degrees of deactivation lead to an irreversible deterioration of the polymer film. Electrochemical Impedance Spectroscopy

applied at negative potential values allowed obtaining dependences of the different transport parameters on the degree of deactivation of the polymer film. While some parameters such as interfacial metal-film and film-solution resistances ($R_{m|f}$, $R_e^{f|s}$, $R_i^{f|s}$), the high-frequency capacitance (C_H) and the redox capacitance (C_p) exhibit a continuous variation without hysteresis between deactivation and reactivation processes within the whole θ_c range, others such as electron and ion diffusion coefficients (D_e, D_i) show not only marked changes of slope from given θ_c values but also hysteresis between consecutive deactivation and reactivation processes. The diffusion rates of the hydroquinone and benzoquinone species across the polymer film are also strongly reduced with the increase in the degree of degradation. This work could be interesting due to the wide range of potential applications of POAP. In this sense, although in practical applications of POAP it is necessary to maintain the conducting properties unaltered, the polymer is subjected to extreme conditions that can cause its partial deactivation. Thus, it seems to be important for electrochemists to know at least how the charge-transport process at POAP films changes with their deactivation.

Chapter 4 - Benzene, declared as an environmental contaminant, has commonly been used as an industrial solvent, a starting material for the synthesis of other chemicals, and as an antiknock agent in gasoline, and is a significant component of cigarette smoke. While not fully understood, the toxicity of benzene is linked to the production of reactive metabolites formed during cytochrome P4502E1. Benzene is metabolized by cytochrome P450 CYP2E1 to benzene oxide, which spontaneously forms phenol. Phenol is converted to hydroquinone by P4502E1. Hydroquinone and related metabolites are converted in the bone marrow, by myeloperoxidase, to benzoquinones, which are potent hematotoxic and genotoxic compounds that undergo further metabolic activation, by one-electron reducing enzymes, to generate semiquinones and reactive oxygen species (ROS). As an excess of ROS is produced, oxidative stress can occur and lead to altered cellular signaling. The production of ROS is tightly regulated and the cell possesses detoxifying mechanisms such as catalase, glutathione and superoxide dismutase to maintain appropriate cellular ROS levels. 1,4 benzoquinone (BQ) can alter signaling pathways and affect chromosomal integrity. Numerous attempts have been made to understand cytotoxic mechanisms influenced by the chemical structure of BQ generate DNA breaks and apoptosis. It is also a strong topoisomerase II poison. Its toxicity is mainly due to oxidative stress and/or forming Michael-type adducts with proteins and glutathione (GSH). Owing to the important physiological roles of quinones, such as hydroquinone,

1,4 benzoquinone, and reduced thiols such as GSH, it is necessary to develop sensitive and selective methods for the measurement of those substances to study cellular mechanisms of chemical-induced toxicity. For this purpose, the benzoquinone (BQ) is used in the electrochemical determination of thiol molecules. The Addition of sulfur nucleophiles to quinones has been studied and Characterized as 1, 4-reductive addition of the Michael type. Quinones, containing a polarized double bond, are considered Michael acceptors, where the Michael donors are thiol nucleophiles. The final product of this reaction is hydroquinone with a sulfur atom in the ortho position. If a metal surface is modified with a dithiol (to form a thiolate with the metal surface, leaving a free thiol,-HS) molecule, the reaction with BQ will be easy to produce hydroquinone (H2Q) moiety. The latter product can be used to determine electrochemically thiol-containing compounds in its structure.

Chapter 5 – Hydroquinone (HQ) is a major benzene metabolite that can be further oxidized toreactive quinones. It has been employed as a component of skin lighters and a photographic reducer.Its adverse effects on different cells have been demonstrated.High concentrations of HQ induces apoptosis in Jurkat cells. It induces DNA and chromosomal damage in mouse fibroblasts.It elicits DNA hypomethylation that accounts for the leukomogenicity of benzene.HQ causes apoptosis in human peripheral white blood cells. It induces oxidative damage anddiminishes expression of human 8-oxo-guanine DNA glycosylase mRNA in human A549lung adenocarcinoma cells. It hinders progression of T cell cycle by suppressingcyclin-dependent kinases. It brigs about alterations in protein expression inhuman hepatocytes. Exposure to HQ in utero causes a decline in the percentage ofdifferentiated HD3 avian erythroblast cells concomitant with a rise in reactiveoxygen species, both of which can be reduced by superoxide dismutase conjugatedto polyethylene glycol. Myeloperoxidase-activated HQ inhibits topoisomerase II,a,

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Chapter 1

INVOLVEMENT OF CIGARETTE SMOKE-RELATED HYDROQUINONE IN THE PATHOGENESIS OF AGE-RELATED MACULAR DEGENERATION

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ABSTRACT

The goal of this chapter is to review the most relevant scientific evidence supporting the role of cigarette smoke-related hydroquinone in the pathogenesis of age-related macular degeneration (AMD), a major cause of blindness among the elderly and to highlight the importance of smoking cessation to reduce the risk for developing AMD. AMD is a late onset (after age 50), progressive degeneration of the retina associated with vision loss coupled with a spectrum of specific clinical, physiological and histopathological features. The early or dry stage of AMD is characterized by the accumulation of drusen, specific lipid rich deposits under the retina whereas the late or wet stage is due to the growth of abnormal new vessels under the retinal pigment epithelium

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(RPE) from the subjacent choroid, termed choroidal neovascularization (CNV). Extracellular matrix turnover (ECM], inflammation, and angiogenesis are key cellular processes that play a central role in the pathogenesis of AMD. The scientific evidences to support the interpretation of the RPE injury by hydroquinone are reviewed in depth, especially the proposed role of hydroquinone on ECM turnover, inflammation, and CNV.

Keywords: Age-related Macular Degeneration, response to injury, reactive oxygen intermediates, blebbing, extracellular matrix turnover, actin cytoskeleton, Hsp25/27, MAPK, sub-RPE deposits, cigarette smoke, hydroquinone, inflammation, angiogenesis, animal model

HYDROQUINONE AND ITS ADVERSE HEALTH EFFECTS

Hydroquinone (benzene-1,4-diol) is an aromatic hydrocarbon metabolite of benzene (Figure 1) and ubiquitous environmental pollutant that has cytotoxic, haematotoxic, immunotoxic, and genotoxic properties [1-4]. It is a white, odorless, crystalline solid moderately soluble in water and highly soluble in alcohol. In the presence of water, hydroquinone can slowly oxidize to quinone, which is more volatile. Hydroquinone is used as a developer in the photographic industry, as an anti-oxidant in the rubber industry and as intermediate in the manufacturing of food antioxidants. It is also used as an ingredient in skin lighteners and is a natural ingredient in many plant-derived products, including fruits, grains, coffee, tea, beer, and wine. Following ingestion, hydroquinone is metabolized to water-soluble compounds in the liver, then filtered by the kidney, and eliminated in the urine. Exposure to hydroquinone from these common foods probably explains the presence of low concentrations of this quinone in the urine and plasma of people who have no occupational or other known exposure to hydroquinone.

Hydroquinone has also been identified in relatively high concentrations in the smoke of non-filtered cigarettes (up to 155 μg per cigarette) [5-7] and nominated for study by the National Cancer Institute based on its high levels of production and potential for human exposure [8]. In addition, hydroquinone is of interest as a metabolite of benzene via a cytochrome p450-mediated pathway [9,10] and as a model for quinone toxicity, since many chemicals and drugs of research interest contain the quinone nucleus [11].

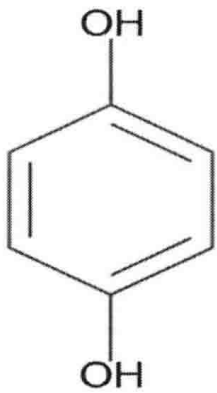

Figure 1. Chemical structure for hydroquinone.

All quinones can be futher bioactivated by myeloperoxidases and other hemo-protein perosidases [12] and become oxidants by a similar mechanism [7, 13, 14]. Hydroquinone competes with the normal substrate of mitochondrial oxidases associated with electron transport, and undergoes redox cycling with its corresponding semiquinone radical. As a result, hydroquinone metabolism in the mitochondria generates superoxide anion, which in turn, damages mitochondrial membranes and leaks into the cytoplasm [12]. In the cytoplasm, superoxide can be converted into hydroxyl anion and hydroxyl radicals. Intracellular hydroquinone-reactive oxygen species (ROS) generation participate in protein oxidation, lipid peroxidation [15], and DNA oxidation and damage [16], considering hydroquinone as the most potent DNA-damaging benzene metabolite and suggesting a role as strong pro-oxidant agent with chemical reactivity.

It has been reported that hydroquinone reacts with sulfhydryl groups of thiol compounds, such as L-cysteine, dithiothreitol, and N-acetyl-L-cysteine [17] and that its reactivity increases in the presence of nitric oxide (NO) [4]. This chemical reactivity appears to depend on the position of hydroxyl groups in the benzene backbone. Hydroxyl groups in the *para* position were confirmed to be the most reactive, since catechol with *ortho* groups and resorcinol with *meta* groups showed reduced inhibitory effects [17]. The effects of hydroquinone may thus occur as the result of direct binding to L-cysteine residues critically involved in the activity of target proteins.

Data from a number of laboratories provide compelling evidence that environmental toxicity of hydroquinone is an important consideration since previous reports have suggested the pathological importance of hydroquinone in the modulation of inflammation [17-19], immune responses [20-25],

apoptosis , nephrotoxicity [26], skin allergy and pigment lightening [27-29], and eye irritation with impairment of vision among others [30, 31].

It has been shown that hydroquinone is toxic to immune-system and bone marrow cells [20, 21]. Thus, in chronic cigarette smokers, hydroquinone may cause increased rates of higher respiratory tract infection probably due to its immunosuppressive effects [20, 21]. According to Cho et al. hydroquinone suppresses most stages of innate immunity mediated by monocytes and macrophages, and of adaptive immunity by lymphocytes, suggesting that the initial activation of macrophages by bacterial infection might be diminished by hydroquinone exposure [22]. Additionally, hydroquinone can inhibit the migration of monocytes from the blood to infected areas and the aggregation of these cells at infection sites, and reduce the normal viability of lymphocytes from bone marrow and spleen [22]. Previous reports have also suggested that hydroquinone mediates allergic diseases via suppression of nuclear factor (NF)-κB binding activity and blockade of interferon IFN-γ and IL-12 production from activated T cells and macrophages respectively supporting an inhibitory role in Th1-type lymphocytes [23–25]. Hydroquinone is also able to cause renal tubular cell degeneration in the renal cortex [8] and induce apoptosis in human embryonic kidney cells through depletion of intracellular thiol [26], to destroy directly cytochrome P450 in human liver [32, 33], and to inhibit melanocyte tyrosinase in skin [34].However, it is important to note that because its potential cancer risk, some countries have banned the use of this compound as skin whitening. Hydroquinone has also been strongly implicated in producing leukemia associated with benzene exposure [35] and carcinogenesis [8]. Other human health effects related to hydroquinone are stimulation of nervous system [36], brown pigment deposition in the conjunctive and structural alterations of the cornea which can impair vision [30, 31]. As we will discuss below, cigarette smoke-related hydroquinone can damage the retina through oxidative processes thereby suggesting a role in the pathogenesis of age-related macular degeneration (AMD).

AGE-RELATED MACULAR DEGENERATION

Age-related macular degeneration (AMD) is a late onset (after age 50), progressive degeneration of the retina associated with vision loss coupled with a spectrum of specific clinical, physiological and histopathological features [37, 38]. AMD affects 30% of people older than age 70, and is the leading cause of blindness in the elderly [39, 40]. Fourteen million people may be

affected in the United States, and over 60 million worldwide. Since the population older than 60 years is the fastest growing segment in western society, the burden of AMD is becoming a huge global public health problem [39, 40].

The clinical presentation of AMD progresses through two stages: early and late [41]. Early AMD ("atrophic" or "dry" degeneration) is characterized by accumulation of drusen and other lipid rich extracellular deposits under the retinal pigment epithelium "(RPE) [41-43]. During aging, deposits initially accumulate between the RPE and its basement membrane (called basal laminar deposit or BLD), but progression into AMD requires additional deposit formation within Bruch's membrane (BrM), (called basal linear deposit (BLiD) and "nodular" drusen). Ultimately, early AMD can progress into late or severe atrophic AMD characterized by death of RPE and photoreceptors (called geographic atrophy) [41, 43] (Figure 2). Late AMD ("exudative" "neovascular" or "wet" degeneration) is characterized by endothelial invasion and pathological neovascularization under the retina [41, 43]. Wet AMD is always preceded by early disease [43]. Death or dysfunction of retinal photoreceptors is the ultimate cause of vision loss [44].

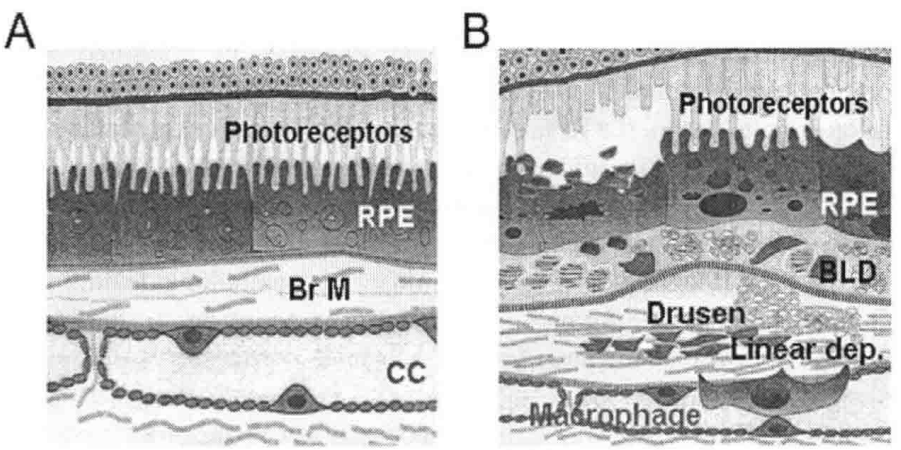

Figure 2. Normal anatomy of the retina (A). Histopathologic changes of early Age-related Macular Degeneration (AMD) (B). The schematic drawing shows the typical sub-Retinal Pigment Epithelium (RPE) deposits located in Bruch's Membrane (BM). Basal laminar deposits (BLD) are normally located between the RPE cell membrane and the RPE basement membrane while basal linear deposits (BLinD) and drusen are located in the inner collagenous layer of BM. Other histologic findings of this early stage of the disease are also shown such as devitalized photoreceptors and RPE cells, BM thickening, and invasion of macrophages. CC= Choriocapillaris.

However, the initial pathogenic target of AMD is the RPE, its extracellular matrix (called BrM), and the subjacent vascular bed [called choriocapillaris], the blood supply for the outer retina [39]. To date, little is known about the pathogenesis of dry AMD and events or factors that convert the dry form of the disease to its wet form. Treatment options currently available are very limited for this major public health concern. As a result, the development of preventive strategies is an area of great importance.

AMD is a multifactorial disease with age, systemic health, genetic and environmental risk factors influencing disease progression [45, 46]. The most important pathogenic factors leading up to AMD include oxidative stress, inflammation, and local production of angiogenic factors [47]. A substantial body of literature suggests a role for oxidant injury to the RPE and local inflammation as putative mechanisms in the pathogenesis of AMD [48-50]. Although intuitively obvious, oxidant injury can induce either lethal responses, leading to cell death, or nonlethal responses inducing a functional change from baseline compatible with continued life of the cell but leading to dysfunction of the tissue or organ. Most studies focus on oxidant-mediated death of RPE [51-54]. Yet, RPE death [so-called geographic atrophy] is a very late stage of dry AMD, resulting from a very chronic and progressive process which involves widespread atrophy of the RPE, inducing apoptosis of overlying photoreceptors and subsequent exposure of choroidal vessels. Subretinal deposits and thickening of BrM, the hallmarks of early AMD, develop decades before the RPE cells actually die. Therefore, nonlethal cellular responses to RPE oxidant injury must contribute to early AMD [6, 55].

Atrophic AMD is the most common form, affecting approximately 85% of persons with AMD. As outlined above the accumulation of specific deposits under the RPE (Figure 3) is a very prominent histopathologic feature of eyes with AMD [56-59]. The formation of drusen is an active process with distinct biological pathways. However, lack of scientific consensus exists regarding the origin of drusen. Research from different groups has been based on the conceptually innovative RPE injury hypothesis which proposes that deposit formation and accumulation is secondary to chronic, repetitive but nonlethal RPE injury RPE [60-66]. Irrespective of the injury, this model proposes that all stimuli result in a final common pathway of cellular responses that cause the actual deposits. Repetitive injury ultimately can kill RPE leading to late dry AMD [67].

More recently, inflammatory-derived injury stimuli have also been implicated, including oxidants, complement, immune complexes and factors produced by macrophages [47, 63, 68].