Predicting the possible metabolites of parabens for hepatotoxicity

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Abstract: *Drug and chemical mediated hepatotoxicity for wide numbers of chemicals has been recognized. The drug mediated hepatotoxicity and its evaluation is an important aspect in the development of drugs intended for therapeutic usages as well as chemicals used as food and cosmetic additive. Parabens are widely used as preservatives in drugs, cosmetic products, and foodstuffs. Safety concerns have recently increased due to the potential health risks associated to exposure to large amounts of these substances. Biotransformation of parabens mainly includes hydrolysis of the ester bond and glucuronidation reactions.*

The aim of this work was to predict the possible metabolites for hepatotoxicity of some parabens by a specialized software.

Key words: *parabens, hepatotoxicity, metabolites*

INTRODUCTION

Dermal exposure study of environmentally available chemicals is a new initiative in the field of toxicology research. This is particularly more relevant in case of chemicals that find its way into human system through skin. Drug and chemical induced liver injury is a serious complication, because liver is central to the metabolic disposition of virtually all drugs and foreign substances. Xenobiotics may be toxic by themselves or their metabolites play an important role in liver injury. The mechanism of hepatocytes toxicity may results either directly from the disruption of intracellular function or membrane integrity or from damages affecting endothelial or bile duct cells as seen in cholastatis or indirectly from immune mediated membrane damage [1].

Parabens are also designated as esters of *p*-hydroxybenzoic acid. The most commonly found parabens are methyl-, ethyl-, propyl- and butylparaben. Parabens are extensively used as antimicrobial preservatives in food, cosmetics and pharmaceutical products due to their broad spectrum of activity, inertness and low cost. Parabens also congregate several criteria for an ideal preservative: they are stable and effective over an extensive pH range, sufficiently soluble in water to produce an effective concentration in aqueous phase, have no perceptible odor or taste, no induction of discoloration and stability over broad pH and heat ranges [10]. Parabens are lipophilic compounds with increasing octanol/water partition coefficients (expressed as log *K*ow) as the carbon number of the alkyl chain of parabens increases. Antimicrobial activity of parabens increases with the length of alkyl grouping from methyl to *n*-butyl [6]. Since microbial replication generally occurs in the water phase of oil/water bases, the amount of paraben dissolved in the water phase generally determines the preservative efficiency; for such reason, in order to increase the ability of the system to withstand microbial contamination, it is common to find combinations of two or more paraben homologues within a single product [3].

Man is daily exposed to these substances from a large array of consumer products, and they are considered to be safe. Several toxicity studies of these compounds have been carried out in animals and in man; no marked toxicity was found as they are rapidly absorbed, metabolized and excreted from the body [12]. However, recent reports indicated that parabens could act as endocrine modulators or disruptors with a moderate estrogenic activity which could lead to possible undesirable effects on human health. Moreover, parabens-containing antiperspirants have been suspected of increasing breast cancer incidence. The detection in small quantities of non-metabolized parabens in human breast tumors [4] may suggest that the substances could accumulate over time in tissues and induce toxic effects [5,13].

Parabens are extensively metabolized. They are mainly hydrolyzed to 4-hydroxybenzoic acid in mammals, which is thereafter conjugated with sulfate, glucuronide or glycine prior to being excreted in urine [14-16]. Esterases are efficient in the hydrolysis

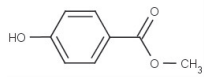
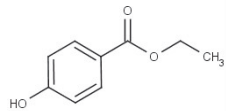
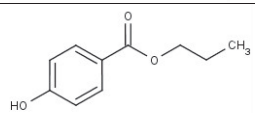
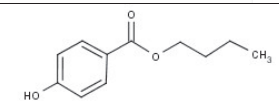
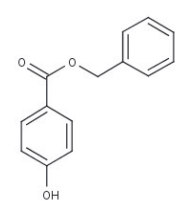
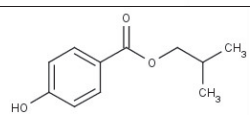
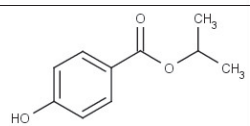
of parabens to 4-hydroxybenzoic acid [7,8]. In man, parabens can also be excreted as glucuronides and sulfate conjugates [12]. The metabolic profile is strongly dependent on the exposure route. Indeed, paraben glucuronides have been used as urinary biomarkers of exposure in man, rather than 4-hydroxybenzoic acid, which is a nonspecific metabolite of all parabens [17].

The aim of this work was to predict the possible metabolites for hepatotoxicity of some parabens by a specialized software.

MATERIALS AND METHODS

Compounds. Some parabens [2] were investigated which are presented in Table 1.

Table 1 CAS number, name and structure of some parabens

№	CAS number	Name of compound	Structure of compound
1	99-76-3	Methyl-p-hydroxybenzoate	
2	120-47-8	Ethyl-p-hydroxybenzoate	
3	94-13-3	Propyl-p-hydroxybenzoate	
4	94-26-8	Butyl-p-hydroxybenzoate	
5	94-18-8	Benzyl-p-hydroxybenzoate	
6	4247-02-3	2-Methylpropyl 4-hydroxybenzoate	
7	4191-73-5	1-Methylethyl-4-hydroxybenzoate	

OECD (Q)SAR Application Toolbox. (Quantitative) Structure-Activity Relationships [(Q)SARs] are methods for estimating properties of a chemical from its molecular structure and have the potential to provide information on the hazards of chemicals, while reducing

time, monetary costs and animal testing currently needed. To facilitate practical application of (Q)SAR approaches in regulatory contexts by governments and industry and to improve their regulatory acceptance, the OECD (Q)SAR project has developed various outcomes such as the principles for the validation of (Q)SAR models, guidance documents as well as the QSAR Toolbox [11].

Metabolic pathways documented for 200 organic chemicals in different mammals are stored in a database format that allows easy computer-aided access to the metabolism information. The collection includes chemicals of different classes, with variety of functionalities such aliphatic hydrocarbons, alicyclic rings, furans, halogenated hydrocarbons, aromatic hydrocarbons and haloaromatics, amines, nitro-derivatives, and multifunctional compounds. *In vivo* and *in vitro* (predominantly, with liver microsomes as experimental systems) studies were used to analyze the metabolic fate of chemicals. Different sources, including monographs, scientific articles and public websites were used to compile the database [9, 11].

RESULTS AND DISCUSSION

The results of the probable metabolic activation in liver (observed and predicted) of some parabens are presented in Table 2.

Table 2 Probable metabolic activation of some parabens by (Q)SAR Application Toolbox

№	Paraben	Observed liver metabolism by Toolbox	Liver Metabolism Simulator by Toolbox
1	Methyl-p-hydroxybenzoate	0 metabolites;	2 metabolites;  1) 2)
2	Ethyl-p-hydroxybenzoate	0 metabolites;	4 metabolites;  1)  2)  3)  4)
3	Propyl-p-hydroxybenzoate	0 metabolites;	4 metabolites;  1)  2)  3)  4)
4	Butyl-p-hydroxybenzoate	0 metabolites;	4 metabolites;  1)  2)

			3)  4) 
5	Benzyl-p-hydroxybenzoate	0 metabolites;	4 metabolites; 1)  2)  3)  4) 
6	2-Methylpropyl 4-hydroxybenzoate	0 metabolites;	4 metabolites; 1)  2)  3)  4) 
7	1-Methylethyl-4-hydroxybenzoate	0 metabolites;	9 metabolites; 1)  2)  3)  4)  5)  6)  7)  8)  9) 

CONCLUSIONS

Parabens are largely used as preservatives in cosmetics, drugs and foodstuffs due to their efficient antibacterial properties. Potential health risks in man as a result of regular exposure have recently been suggested, although these substances have been considered safe because their extensive metabolism prevents them from accumulating in tissues. The possible estrogenic hazard of parabens is still a much-debated question. Such a hazard may, however, be affected by the metabolism and elimination rates of these substances, which are dose, route and species dependent.

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The paper is reviewed.