

Short Communication

Computational Assessment of Biological Effects of Methyl-, Ethyl-, Propyl- and Butyl-Parabens

Marin Roman, Diana Larisa Roman, Vasile Ostafe, and Adriana Isvoran*

Department of Biology-Chemistry and Advanced Environmental Research Laboratories, West University of Timisoara, Romania

*Corresponding author

Adriana Isvoran, Department of Biology-Chemistry and Advanced Environmental Research Laboratories, West University of Timisoara, 16 Pestalozzi, 300115 Timisoara, Romania, Tel: 40256592634; Fax: 40256592620; Email: adriana.isvoran@e-uvf.ro

Submitted: 05 April 2018

Accepted: 10 May 2018

Published: 12 May 2018

ISSN: 2576-1102

Copyright

© 2018 Isvoran et al.

OPEN ACCESS

Keywords

- Parabens
- ADME-tox profiles
- Biological activities
- Toxicity
- Molecular docking

Abstract

Within this study we have used a computational approach to predict the ADME-Tox profiles, the pharmacokinetics properties and the biological effects of the most used parabens: methylparaben (MP), ethylparaben (EP), propylparaben (PP) and butylparaben (BP). Our results expose that all investigated parabens reveal good oral bioavailability and skin permeation meaning that they are rapidly absorbed and are able to reach the systemic circulation. They are also able to penetrate the blood brain barrier and consequently to affect the central nervous system. Investigated parabens reflect different degrees of toxicity, PP and BP revealing higher toxic effects. Our study also suggests that investigated parabens reveal no carcinogenicity and mutagenicity, a weak potential to inhibit the hERG channel and are able to inhibit human CYPs, BP having the higher inhibitory potential. CYPs inhibition by parabens affects the metabolism of numerous endogenous and exogenous compounds and may cause significant xenobiotics interactions.

ABBREVIATIONS

PB: Parabens; ADME-Tox: Absorption Distribution Metabolization Excretion and Toxicity; MP: Methylparaben; EP: Ethylparaben; PP: Propylparaben; BP: Butylparaben; IUPAC: International Union of Pure and Applied Chemistry; SMILES: Simplified Molecular-Input Line-Entry System; SDF: Structure-Data File; GI: Gastrointestinal Absorption; BBBP: Blood Brain Barrier Permeation; P-gp: P-glycoprotein; LogKp: Skin Permeation Coefficient; hERG: The Alpha Subunit of the Potassium Ion Channel.

INTRODUCTION

Parabens define a collective term for *p*-hydroxybenzoic acid esters being obtained by distinct chemical substitutions at the para position of the benzene ring. The substituent could be linear or branched, the chemical substitutions providing different properties of resulting parabens [1].

Parabens have antibacterial and antifungal properties and are broadly used as preservatives in cosmetics, pharmaceuticals, food and beverage processing due to their broad spectrum of activity, inertia and low cost. The popularity of parabens is due to their numerous beneficial properties such as: low sensitivity

or irritation frequency, high chemical stability over wide ranges of pH and temperature, hydrolysis resistance, lack of changes in product consistency or coloration, biodegradability and low cost production [2,3].

There are literature data evidencing that parabens are present in some food and beverages, pharmaceuticals, cosmetics and personal care products [4-7]. Therefore, people which are using these products, especially those involved in their production and packaging, are exposed to parabens by ingestion, inhalation and/or skin absorption. Specific literature emphasizes the presence of parabens in urine [8-12] and blood samples [13,14] of humans. These data advocate that paraben exposure is omnipresent and further evaluation of potential health risk of these chemicals is necessary.

It has been revealed that most parabens are rapidly metabolized into *p*-hydroxybenzoic acid by esterases and are excreted in the form of salt and other metabolites [15]. However, part of parabens may not undergo hydrolysis and a definite quantity of unmetabolized compounds may remain systemically available [7,12,14]. Within this study we only consider the non-metabolized parabens and do not take into account their biotransformation and the hydrolyzed/conjugated forms:

methylparaben (MP), ethylparaben (EP), propylparaben (PP) and butylparaben (BP). These compounds are presented in Table (1).

Investigated parabens are relatively inexpensive and believed to have low levels of toxicity, irritation and sensitizing potential [3]. Official reports published for MP, EP, PP and BP conducted to conclusion that these compounds are safe as cosmetic ingredients in specified quantities and practices of use [16]. Even if the parabens are generally considered safe, there are published data revealing controversial results. Literature data emphasize that some parabens may stimulate tumor cell proliferation in humans [17,18], may cause respiratory allergies, toxicity and hormonal disorders [19], premature aging of the skin and destruction of DNA of the epithelial cells [20]. Other studies reveal that parabens and their metabolites have endocrine disruptor potential [21-25]. An *in vitro* study on the human lymphocyte cells revealed parabens may expose genotoxic potential [26]. The health effects of parabens in humans are not clear, available data resulted from studies in animals and/or cell cultures and conduct to doubtful conclusions. As it is difficult to find subjects for such studies, we have used a computational approach to predict the biological effects of the most commonly used parabens.

The aim of the present study is to predict the absorption, distribution, metabolization, excretion and toxicity (ADME-Tox) profiles, pharmacokinetic characteristics, the biological activity spectra and the toxicological and/or side effects of the investigated parabens, to assess the predicted interactions by molecular docking and to correlate these predictions with available literature data.

MATERIALS AND METHODS

Structural information concerning the investigated parabens

Structural information concerning the considered compounds that is needed for the further computational analysis has been extracted from ZINC database [27]. The structure of every chemical compound may be represented in different formats and every computational tool use one of these formats. Consequently, distinct formats of the structural data of investigated parabens have been extracted: the simplified molecular-input line-entry system (SMILES), structure-data file (SDF) and MOL2, respectively.

Prediction of ADME-Tox profiles, pharmacokinetics properties and biological effects

FAF-Drugs4tool [28] has been used to assess the achievement of: (i) rules addressing the oral availability: Lipinski's rule [29], Veber's rule [30], Egan's rule [31] and Bayer Oral Physchem Score [32]; (ii) safety profile: GSK rule [33], Pfizer's rule [34], phospholipidosis inducer [35] and Lilly Med Chem rules [36] for each considered paraben.

Swiss ADME tool [37] has been used to predict the passive human gastrointestinal absorption (GI), penetration of the blood-brain barrier (BBBP), skin penetration and inhibition of the human cytochromes (CYPs) mostly involved in the metabolism of xenobiotics: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4.

The same pharmacokinetic properties have been predicted using admetSAR, a large database providing lot of estimation by ADME-Tox profiles of different compounds [38]. The results obtained using Swiss ADME and admetSAR were compared. AdmetSAR also envisages toxicological endpoints such as carcinogenicity, mutagenicity and hERG channel-blocking potential [38]. ToxTree software [39] has been used for accomplishing predictions concerning carcinogenicity and mutagenicity. The biological activity spectra and side effects of investigated compounds are predicted using PASS online tool [40].

Assessment of the predicted molecular interactions

In order to further evaluate the inhibition of CYPs by investigated parabens, molecular docking approach has been used to assess their interactions with the human CYPs. Structures of parabens are extracted from ZINC database [27] and structural files of the cytochromes are extracted from Protein Data Bank [41]: 2HI4 for CYP1A2, 4NZ2 and 5A5I for CYP2C9, 4GQS for CYP2C19, 4XRZ and 4XXS for CYP2D6, 2J0D and 4D6Z for CYP3A4. Only the A chain is considered when more than one chain is present in the crystallographic structure. Chimera software [42] has been used to prepare the structural files for molecular docking (ligands excepting hem are removed, hydrogens and charges are added) and to visualize and analyze the molecular docking results. SwissDock computational utility [43] that is based on EADock algorithm [44], has been used to implement the molecular docking study. A blind, rigid and accurate docking has been considered. From this reason, in order to take into account the enzyme flexibility, in the molecular docking calculations we have considered more than one crystallographic structure for the same cytochrome when available.

Specific literature is abundant in computational tools that may be used to predict bioavailability, safety and biological effects of chemical compounds. We have used the specified tools taking into consideration their accuracy for prediction (higher than 70%) and their user-friendly interfaces.

RESULTS AND DISCUSSION

Results concerning the ADME-Tox profiles of investigated parabens obtained using FAFDrugs4 tool illustrate that all rules regarding the oral bioavailability are respected, but Pfizer's rule

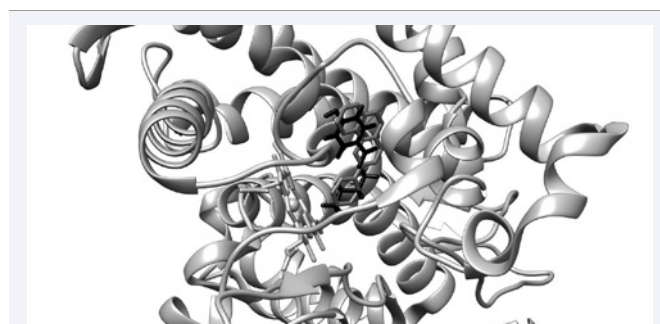


Figure 1 Illustration of the molecular docking result concerning the interaction of butylparaben (black sticks) with CYP1A2 (light grey cartoon): BP binds to the active site of CYP1A2 in the same position as alpha-naphthoflavone (dim grey sticks), the inhibitor that is present in crystallographic structure of CYP1A2.

addressing the safety of compounds is partly respected by MP and EP and violated by PP and BP (Table 2). Taking into account all results presented in Table (2), investigated parabens comply with almost all the rules imposed by filtering and do not contain high risk toxic groups. The EU Scientific Committee on Consumer Safety established that MP, EP, PP and BP are safe at the maximum authorized concentrations [45] Table (2).

The outcomes of SwissADME and admetSAR predictions are summarized in Tables (3,4). They coincide in respect to GI, BBBP and P-gp substrate, but there are some divergences between the predictions considering the inhibition of CYPs. All considered parabens are predicted to have high gastrointestinal absorption, to be able to penetrate the blood brain barrier and not being substrates of P-gp protein (Table 3), meaning that their systemic exposure is low. These predictions are in agreement with few available studies concerning human oral administration of MP and PP conducting to fast absorption and fast metabolism [7, 46] Table (3).

The skin permeability coefficients (logKp, illustrating the transport of compounds through mammalian epidermis) of investigated parabens are comparable with that of diclofenac (logKp=-4.96 cm/s) [37] and it illustrates their capacity to penetrate skin (Table 3). It is an important observation as they are mostly used in cosmetic products. It must be noticed that we did not consider that parabens are partially metabolized in the skin layers and we did not filter their hydrolyzed/conjugated forms. Our findings are in good agreement with literature data revealing that parabens contained into certain skin-care products are rapidly absorbed through the skin into the human body [7, 47-49].

The predictions considering the inhibition of CYPs by parabens obtained using SwissADME and admetSAR respectively,

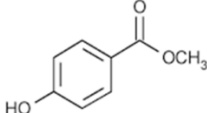
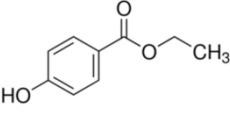
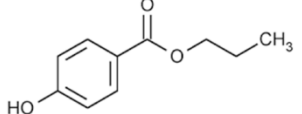
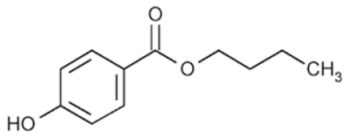
are not similar. Both SwissADME and admetSAR tools predict that MP and EP do not inhibit human CYPs. SwissADME predicts that BP is able to inhibit CYP1A2 and admetSAR predicts that PP and BP are able to inhibit both CYP1A2 and CYP2C19 (Table 4). Taking into account the inconsistency of the predictions made by SwissADME and admetSAR, we have assessed the interactions of all investigated parabens with CYPs using the molecular docking approach implemented under SwissDock server [43]. The results are shown in Table (4).

Molecular docking study emphasizes that all investigated parabens are predicted to bind to the active sites of the human CYPs, the most favorable interactions being obtained for CYP1A2. It reflects that parabens could have inhibitory effects on these enzymes, BP being a more potent CYPs inhibitor than other studied compounds. Figure (1) illustrates the result provided by SwissDock concerning the evaluation of the interaction of BP (black sticks) with CYP1A2 (grey cartoon). It reveals that BP is able to bind to the active site of CYP1A2. BP binds to CYP1A2 in the same position as alpha-naphthoflavone (light grey sticks), the inhibitor that is present in the crystallographic structure of the enzyme Figure (1).

The inhibitory potential of parabens on CYP isoforms has been observed in an *in vitro* study using rat liver microsomes as the enzyme source [50]. The interactions of parabens with human CYPs may affect the binding of other endogenous (hormones) or exogenous compounds (especially drugs) to CYPs influencing the drug metabolism and increasing the side effects of drugs.

Both Toxtree and admetSAR computational tools revealed that all investigated parabens provided not nongenotoxic carcinogenicity, genotoxic carcinogenicity and mutagenicity and they reflect a weak potential to inhibit the hERG potassium channels that are essential for normal electrical activity in the

Table 1: Parabens considered in this study.

Paraben	IUPAC name	Chemical structure
methylparaben	methyl 4-hydroxybenzoate	
ethylparaben	ethyl 4-hydroxybenzoate	
propylparaben	propyl 4-hydroxybenzoate	
butylparaben	butyl 4-hydroxybenzoate	

Abbreviation: IUPAC - International Union of Pure and Applied Chemistry.

Table 2: ADME-Tox profiles of considered parabens obtained using FAFDrugs4 tool: light grey boxes illustrate that corresponding rules are respected, dark grey boxes denote rules that are partially respected and black boxes illustrate rules that are entirely broken.

Parabens name	ADME-ToxProfile							
	Oral Bioavailability				Safety Profiling			
	Lipinski Rule	Veber Rule	Egan Rule	Bayer Oral Physchem Score	GSK 4/400 Rule	Pfizer 3/75 Rule	Phospholipidosis Inducer	Lilly Med Chem Rules
Methylparaben								
Ethylparaben								
Propylparaben								
Butylparaben								

Abbreviations: ADME-Tox: Absorption, Distribution, Metabolization, Excretion, Toxicity

Table 3: Pharmacokinetics of considered parabens predicted using SwissADME and admetSAR computational tools.

Paraben name	GI		BBBP		P-gp substrate		Swiss ADME LogKp (cm/s)
	Swiss ADME	admet SAR	Swiss ADME	admet SAR	Swiss ADME	admet SAR	
Methylparaben	Yes	Yes	Yes	Yes	No	No	-4.95
Ethylparaben	Yes	Yes	Yes	Yes	No	No	-5.24
Propylparaben	Yes	Yes	Yes	Yes	No	No	-5.56
Butylparaben	Yes	Yes	Yes	Yes	No	No	-5.84

Abbreviations: GI: Gastrointestinal Absorption; BBBP: Blood-Brain Barrier Permeation; P-gp: P-glycoprotein; Log Kp: skin permeation coefficient.

Table 4: Predictions concerning the inhibition of the cytochromes mainly involved in the metabolism of xenobiotics by considered parabens.

Parabens/ CYP inhibition	Methylparaben	Ethylparaben	Propylparaben	Butylparaben
CYP1A2 inhibitor	SwissADME	No	No	Yes
	admetSAR	No	No	Yes
	SwissDock (ΔG kcal/mol)	-7.00	-7.31	-7.85
CYP2C9 inhibitor	SwissADME	No	No	No
	admetSAR	No	No	No
	SwissDock (ΔG kcal/mol)	-6.24	-6.11	-6.87
CYP2C19 inhibitor	SwissADME	No	No	No
	admetSAR	No	No	Yes
	SwissDock (ΔG kcal/mol)	-6.42	-6.70	-7.31
CYP2D6 inhibitor	SwissADME	No	No	No
	admetSAR	No	No	No
	SwissDock (ΔG kcal/mol)	-5.66	-5.48	-6.45
CYP3A4 inhibitor	SwissADME	No	No	No
	admetSAR	No	No	No
	SwissDock (ΔG kcal/mol)	-6.48	-6.73	-7.09

Abbreviations: CYP: Human Cytochrome.

heart (data not shown). *In vitro* and animal studies also reflected non carcinogenic and non-mutagenic effects of parabens [46,51,52]. It must be specified that we did not take into account the accumulation of parabens and the possible synergic effects of the presence of more than one paraben (or other exogenous chemical compounds) in the human body.

The outcomes of the PASS Online tool show that investigated parabens reflect a broad spectrum of biological activities being possible inhibitors for many enzymes and having few side effects: ulcer, muscle weakness, eye and skin irritation and apnea (data not shown). Skin irritation has been observed for MP *in vivo* [53] and an *in vitro* study revealed that the rate of allergic contact dermatitis produced by MP in humans is low [54]. Furthermore, other studies confirmed the inhibitory effects of parabens on some enzymes [46,55].

CONCLUSION

Within this study we have predicted the biological activities and side effects of parabens in humans. Our study confirmed that investigated parabens reveal good oral bioavailability and good skin permeation illustrating that they are rapidly absorbed into the human body and reach the systemic circulation. Parabens are predicted as being able to penetrate the blood brain barrier and, consequently, they may affect the central nervous system.

Investigated parabens reveal no carcinogenicity and mutagenicity and a weak potential to inhibit the hERG channel. On the contrary, they are able to inhibit the human CYPs, BP having the higher inhibitory potential. CYPs inhibition by parabens affects the metabolism of numerous endogenous and exogenous compounds and causes significant xenobiotics interactions. As humans are exposed to many types of xenobiotics (phthalates, food additives, pesticides, etc.), their interactions with CYPs contribute to a broad range of health problems in humans.

The great majority of the results that we have obtained in this study are in good agreement with published data obtained through *in vitro* and/or on animal experiments. All these results are important for people awareness, especially for those that are professionally exposed to high amount of parabens. The results obtained by computational tools can complete the *in vivo* toxicity tests to improve predictive toxicity and safety assessment of parabens.

REFERENCES

- Sasseville D. Hypersensitivity to preservatives. *Dermatol Ther.* 2004; 17: 251-263.
- Witorsch RJ, Thomas JA. Personal care products and endocrine disruption: A critical review of the literature. *Crit Rev Toxicol.* 2010; 40: 1-30.
- Majewska N, Zareba I, Surazynski A, Galicka A. Methylparaben-induced decrease in collagen production and viability of cultured human dermal fibroblasts. *J Appl Toxicol.* 2017; 37: 1117-1124.
- Błędzka D, Gromadzińska J, Wąsowicz W. Parabens. From environmental studies to human health. *Environ Int.* 2014; 67: 27-42.
- Moreta C, Tena MT, Kannan K. Analytical method for the determination and a survey of parabens and their derivatives in pharmaceuticals. *Environ Res.* 2015; 142: 452-460.
- E Hussein S, Muret P, Berard M, Makki S, Humbert P. Assessment of principal parabens used in cosmetics after their passage through human epidermis-dermis layers (ex-vivo study). *Exp Dermatol.* 2007; 16: 830-836.
- Francisco A, Fonseca AP. Parabens paradoxes in cosmetic formulations: A review. *Int J Med Res Pharm Sci.* 2016; 3: 1-11.
- Adoamnei E, Mendiola J, Monino-Garcia M, Vela-Soria F, Iribarne-Duran LM, Fernandez MF et al. Urinary concentrations of parabens and reproductive parameters in young men. *Sci Total Environ.* 2018; 621: 201-209.
- Honda M, Robinson M, Kannan K. Parabens in human urine from several Asian countries, Greece, and the United States. *Chemosphere.* 2018; 201: 13-19.
- Kim S, Lee S, Shin C, Lee J, Kim S, Lee A et al. Urinary parabens and triclosan concentrations and associated exposure characteristics in a Korean population-A comparison between night-time and first-morning urine. *Int J Hyg Environ Health.* 2018; 1438 : 30796-30804.
- Minguez-Alarcon L, Chiu YH, Messerlian C, Williams PL, Sabatini ME, Toth TL et al. Urinary paraben concentrations and *in vitro* fertilization outcomes among women from a fertility clinic. *Fertil Steril.* 2016; 105: 714-721.
- Ye X, Bishop AM, Reidy JA, Needham LL, Calafat AM. Parabens as urinary biomarkers of exposure in humans. *Environ Health Perspect.* 2006; 114: 1843-1846.
- Frederiksen H, Jorgensen N, Andersson AM. Parabens in urine, serum and seminal plasma from healthy Danish men determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS). *J Expo Sci Environ Epidemiol.* 2011; 21: 262-271.
- Azzouz A, Rascon AJ, Ballesteros E. Simultaneous determination of parabens, alkylphenols, phenylphenols, bisphenol A and triclosan in human urine, blood and breast milk by continuous solid-phase extraction and gas chromatography-mass spectrometry. *J Pharm Biomed Anal.* 2016; 119: 16-26.
- Raza N, Kim KH, Abdullah M, Raza W, Brown RJC. Recent developments in analytical quantitation approaches for parabens in human-associated samples. *TrAC Trends in Analytical Chemistry.* 2018; 98: 161-173.
- Boyer IJ, Becker LC. Safety Assessment of Parabens as Used in Cosmetics. *Cosmetic Ingredient Review.* 2017
- Darbre PD, Byford JR, Shaw LE, Hall S, Coldham NG, Pope GS, et al. Oestrogenic activity of benzylparaben. *J Appl Toxicol.* 2003; 23: 43-51.
- Pan S, Yuan C, Tagmount A, Rudel RA, Ackerman JM, Yaswen P, et al. Parabens and human epidermal growth factor receptor ligand cross-talk in breast cancer cells. *Environ Health Perspect.* 2016; 124: 563-569.
- Darbre PD, Harvey PW. Paraben esters: review of recent studies of endocrine toxicity, absorption, esterase and human exposure, and discussion of potential human health risks. *J Appl Toxicol.* 2008; 28: 561-578.
- Crinnion WJ. Toxic effects of the easily avoidable phthalates and parabens. *Altern Med Rev.* 2010; 15: 190-196.
- Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, Hauser R, Prins GS, Soto AM, et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. *Endocr Rev.* 2009; 30: 293-342.
- Zoeller RT, Brown TR, Doan LL, Gore AC, Skakkebaek NE, Soto AM, et al. Endocrine-disrupting chemicals and public health protection: a statement of principles from The Endocrine Society. *Endocrinology.* 2012; 153: 4097-4110.

23. Roig B, Mnif W, Hadj Hassine AI, Zidi I, Bayle S, Bartegi A, et al. Endocrine Disrupting Chemicals and Human Health Risk Assessment: A Critical Review. *Critical Reviews in Environmental Science and Technology*. 2013; 43: 2297-2351.
24. Boberg J, Taxvig C, Christiansen S, Hass U. Possible endocrine disrupting effects of parabens and their metabolites. *Reprod Toxicol*. 2010; 30: 301-312.
25. Nowak K, Ratajczak Wrona W, G rska M, Jablonska E. Parabens and their effects on the endocrine system. *Molecular and Cellular Endocrinology*. 2018; in press.
26. Güzel Bayülken D, Ayaz Tüylü B, Sinan H, Sivas H. Investigation of genotoxic effects of paraben in cultured human lymphocytes. *Drug Chem Toxicol*. 2017: 1-8.
27. Irwin JJ, Sterling T, Mysinger MM, Bolstad ES, Coleman RG. ZINC: a free tool to discover chemistry for biology. *J Chem Inf Model*. 2012; 52: 1757-1768.
28. Lagorce D, Bouslama L, Becot J, Miteva MA, Villoutreix BO. FAF-Drugs4: free ADME-tox filtering computations for chemical biology and early stages drug discovery. *Bioinformatics*. 2017; 33: 3658-3660.
29. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Deliv Rev*. 2001; 46: 3-26.
30. Veber DF, Johnson SR, Cheng HY, Smith BR, Ward KW, Kopple KD. Molecular properties that influence the oral bioavailability of drug candidates. *J Med Chem*. 2002; 45: 2615-2623.
31. Egan WJ, Merz KM Jr, Baldwin JJ. Prediction of drug absorption using multivariate statistics. *J Med Chem*. 2000; 43: 3867-3877.
32. Lobell M1, Hendrix M, Hinzen B, Keldenich J, Meier H, Schmeck C, et al. In silico ADMET traffic lights as a tool for the prioritization of HTS hits. *ChemMedChem*. 2006; 1: 1229-1236.
33. Gleeson MP. Generation of a Set of Simple, Interpretable ADMET Rules of Thumb. *J Med Chem*. 2008; 51: 817-834.
34. Hughes JD, Blagg J, Price DA, Bailey S, DeCrescenzo GA, Devraj RV et al. Physiochemical drug properties associated with in vivo toxicological outcomes. *Bioorganic & Medicinal Chemistry Letters*. 2008; 18: 4872-4875.
35. Lagorce D, Sperandio O, Galons H, Miteva MA, Villoutreix BO. FAF-Drugs2: free ADME/tox filtering tool to assist drug discovery and chemical biology projects. *BMC Bioinformatics*. 2008; 9: 396.
36. Bruns RF, Watson IA. Rules for identifying potentially reactive or promiscuous compounds. *J Med Chem*. 2012; 55: 9763-9772.
37. Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Sci Rep*. 2017; 7: 42717.
38. Cheng F, Li W, Zhou Y, Shen J, Wu Z, Liu G, et al. admetSAR: a comprehensive source and free tool for assessment of chemical ADMET properties. *J Chem Inf Model*. 2012; 52: 3099-3105.
39. Benigni R, Bossa C, Jeliaskova N, Netzeva T, Worth A. The Benigni / Bossa rulebase for mutagenicity and carcinogenicity a module of Toxtree. *JRC Sci Tech Rep*. 2008.
40. Poroikov V, Filimonov D, Lagunin A, Glorizova T, Zakharov A. PASS: identification of probable targets and mechanisms of toxicity. *SAR QSAR Environ Res*. 2007; 18: 101-110.
41. Berman HM, Westbrook J, Feng Z, Gilliland G, Bhat TN, Weissig H, et al. The Protein Data Bank. *Nucleic Acids Research*. 2000; 28: 235-242.
42. Pettersen EF, Goddard TD, Huang CC, Couch GS, Greenblatt DM, Meng EC, et al. UCSF Chimera--a visualization system for exploratory research and analysis. *J Comput Chem*. 2004; 25: 1605-1612.
43. Grosdidier A, Zoete V, Michielin O. SwissDock, a protein-small molecule docking web service based on EADock DSS. *Nucleic Acids Res*. 2011; 39: 270-277.
44. Grosdidier A, Zoete V, Michielin O. EADock: docking of small molecules into protein active sites with a multiobjective evolutionary optimization. *Proteins*. 2007; 1010-1025.
45. Sasseville D, Alfalah M, Lacroix JP. "Parabenoia" Debunked, or "Who's Afraid of Parabens?". *Dermatitis*. 2015; 26: 254-259.
46. C.f.H.M.P. Reflection paper on the use of methyl- and propylparaben as excipients in human medicinal products for oral use. Committee for Human Medicinal Products. 2017.
47. Darbre PD, Harvey PW. Parabens can enable hallmarks and characteristics of cancer in human breast epithelial cells: a review of the literature with reference to new exposure data and regulatory status. *J Appl Toxicol*. 2014; 34: 925-938.
48. Konduracka E, Krzemieniecki K, Gajos G. Relationship between everyday use cosmetics and female breast cancer. *Pol Arch Med Wewn*. 2014; 124: 264-269.
49. Janjua NR, Mortensen GK, Andersson AM, Kongshoj B, Skakkebaek NE, Wulf HC. Systemic uptake of diethyl phthalate, dibutyl phthalate, and butyl paraben following whole-body topical application and reproductive and thyroid hormone levels in humans. *Environ Sci Technol*. 2007; 41: 5564-5570.
50. Ozaki H, Sugihara K, Watanabe Y, Ohta S, Kitamura S. Cytochrome P450-inhibitory activity of parabens and phthalates used in consumer products. *J Toxicol Sci*. 2016; 41: 551-560.
51. Golden R, Gandy J, Vollmer G. A review of the endocrine activity of parabens and implications for potential risks to human health. *Crit Rev Toxicol*. 2005; 35: 435-458.
52. Cosmetic Ingredient Review. Final amended report on the safety assessment of methylparaben, ethylparaben, propylparaben, isopropylparaben, butylparaben, isobutylparaben, and benzylparaben as used in cosmetic products. *Int J Toxicol*. 2008; 27: 1-82.
53. Shaw T, Simpson B, Wilson B, Oostman H, Rainey D, Storrs F. True photoallergy to sunscreens is rare despite popular belief. *Dermatitis*. 2010; 21: 185-198.
54. Ishiwatari S, Suzuki T, Hitomi T, Yoshino T, Matsukuma S, Tsuji T. Effects of methyl paraben on skin keratinocytes. *J Appl Toxicol*. 2007; 27: 1-9.
55. Dumas I, Diorio C. Estrogen pathway polymorphisms and mammographic density. *Anticancer Res*. 2011; 31: 4369-4386.

Cite this article

Roman M, Roman DL, Ostafe V, Isvoran A (2018) Computational Assessment of Biological Effects of Methyl-, Ethyl-, Propyl- and Butyl-Parabens. *J Bioinform, Genomics, Proteomics* 3(1): 1029.