Predictive Analysis of the Pharmacokinetic and Toxicological Endpoints of Naphthalene and its Derivatives

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Abstract

The study was conducted to determine the putative pharmacokinetic and toxicological properties of naphthalene and its derivatives, hence determining their harmful effects, if any in the normal daily function of the human system. The effects of these compounds on hormonal homeostasis and the endocrine system were also evaluated. The pharmacokinetic ADMET (Absorption, distribution, metabolism, excretion, and toxicity) properties were determined by running a computer-simulated prediction on the compounds based on their canonical SMILES (Simplified Molecular Input Line Entry System) structure using the pkCSM online prediction tool. The Canonical SMILES structures were obtained from the PubChem database. The predictive endocrine disruption potential was evaluated using the Endocrine Predictome computational tool which uses a molecular docking system to predict the interaction between the investigated chemicals and the affected nuclear receptors. The results showed that naphthalene and the derivatives have relatively high log P values, implying their respective lipophilicity; however, only naphthalene-1,2,6,7-tetrol could not permeate the blood-brain barrier. Moreover, all the selected compounds are substrates of the P-glycoprotein and do not inhibit their activity. The results also indicated that naphthalene and all four selected derivatives could have an inhibitory effect on the CYP1A2 enzyme and a disruptive effect on some endocrine functions due to their respective high binding affinity with endocrine receptors. In conclusion, the study showed that naphthalene and the derivatives could have adverse effects on the physiological function of the body vis-à-vis neurological damages, and various metabolic disorders. The predictive influence on the endocrine system also indicated the selected chemicals could induce detrimental changes in endocrine functions.

Introduction

The endocrine system is a physiological control system comprising of various ductless glands that secrete hormones which act as messengers that coordinate communications between cells. The system controls metabolic processes, growth and development as well as reproductive functions. The disrupting effects of certain chemicals on the endocrine functions have extensively gained interest in human physiopathology. These chemicals commonly called the endocrine-disrupting chemicals (EDCs) are synthetic and natural compounds that could alter various functions of the endocrine system (Henley and Korach 2006). Every organ of the endocrine system may be a target for the EDCs. Mechanistically, the effects of EDC on the normal human physiology could be genomic or non-genomic; it could also occur through a receptor linked or a nonreceptor linked pathway (Maqbool, et al. 2016). Their respective tendencies to interact with the endocrine receptors have been documented as the major mechanisms of the EDCs (Gore, et al. 2015). These receptors could be membrane-bound receptors or intracellular transcription factors that can be activated by the binding of a corresponding hormone and exert positive or negative effects on the physiopathological processes. The EDCs have been reported to be involved in many chronic diseases like cardiovascular problems, diabetes, reproductive disorder, cancer, and diseases of the nervous system (Wolff, et al. 2000; Uemura, et al. 2009; Alonso-Magdalena, et al. 2010; Lind and Lind 2011). Various sources of the EDCs include industrial, agricultural, and residential source. Examples

of industrial EDCs include polychlorinated biphenyls and alkylphenols. Pesticides, herbicides, and insecticides are examples of agricultural EDCs while phthalates, naphthalene, and bisphenol A are residential EDCs (Kabir et al., 2015; Monneret 2017).

Naphthalene is a bicyclic aromatic hydrocarbon compound that exists primarily as a vapour and commonly exposed to in the homes as insect repellent product in form of mothballs, toilet deodorant blocks, and outdoor air as a product of natural combustion through automobile exhaust and fossil fuel (Preuss, Angerer and Drexler 2003). It is used commercially in the production of polyvinyl chloride plastics, dyes, resins, and the leather tanning agents. 1-Methylnaphthalene (1-MN) and 2-methylnaphthalene (2-MN) are examples of naphthalene derivatives that could also contribute to environmental concentrations of naphthalene-related toxicants. They are present in wood smoke, asphalt, and tar. They are also used in the production of other chemicals such as dyes, and resins. Other derivatives of naphthalene include naphthalene-1,2-diol, and naphthalene-1,2,6,7-tetrol. Naphthalene and its derivatives have been shown to undergo metabolic transformation through the activities of cytochrome P450 enzymes to generate reactive metabolites which are capable of eliciting various disorders including oxidative stress (Lin, et al. 2006; Fukami, et al. 2008).

Exposures to naphthalene and its derivatives had been associated through various studies with poisoning, induction of adverse physiological changes, morbidity and mortality (Feuillet et al., 2006). Despite numerous reports on the related toxicities of naphthalene and its derivatives on human, their mode of toxicities concerning pharmacokinetics and endocrine disruption is substantially less understood. Thus, this study aimed at investigating the predictive pharmacokinetic and toxicological endpoints of naphthalene and its derivatives.

Methodology

Pharmacokinetics

The toxicity risks of naphthalene, 1-methylnaphthalene, 2-methylnaphthalene, naphthalene-1,2-diol, and naphthalene-1,2,6,7-tetrol were predicted based on their ADMET profile. The ADMET (absorption, distribution, metabolism, elimination, and toxicity) studies were predicted using pkCSM tool (http://biosig.unimelb.edu.au/pkcsm/prediction) (Pires et al., 2015). The SMILE molecular structures of the compounds were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov).

Endocrine Disruption

Endocrine disruption potential of the selected chemicals was evaluated using ENDOCRINE DISRUPTOME computational tool (http://endocrinedisruptome.ki.si/) (Kolsek et al., 2014). It uses the molecular docking approach based on AutoDock Vina algorithm to predict the interactions between the investigated chemicals and human nuclear receptors: androgen receptor, oestrogen receptors α and β, glucocorticoid receptor, liver X receptors α and β, peroxisome proliferator-activated receptors α, β/δ and γ, retinoid X receptor α and thyroid receptors α and β.

Results

ADME-Tox Properties of Naphthalene and its Derivatives

The data represented in Table 1 indicates that naphthalene has a molecular weight of 128.174 g/mol. Its positive logarithm of the partition coefficient (logP) (2.8398) shows that it demonstrates more affinity for the lipid phase, meaning it is lipophilic. This means that naphthalene will be slowly metabolized and will be readily absorbed by the body of the patient. Its water solubility is further evidence of its hydrophobic nature, making it very insoluble in water, and harder to metabolize. Naphthalene shows a high Caco-2 permeability at 1.574., meaning it has a high level of absorption when administered or ingested orally and its intestinal absorption in humans is very high at 95.157%. Naphthalene is predicted to have a Skin Permeability value of (-1.433) log Kp, meaning it has relatively low penetration through skin, and a person is not really at risk of dermal penetration from naphthalene. Naphthalene is a P-glycoprotein substrate, meaning P-glycoprotein can bind to it to keep it from entering into the cell. Hence, naphthalene does not inhibit the mediated transport of compounds by any of the P-glycoproteins (I and II). Furthermore, naphthalene-1,2-diol has a molecular weight of 160.172 g/mol. It has a positive logP (2.251) meaning that it demonstrates a relatively-lower affinity for the lipid phase than naphthalene. As in the case of naphthalene, this means that naphthalene-1,2-diol will be slowly metabolized and will be readily absorbed by the body of the patient. Its water solubility is further evidence of its hydrophobic nature, making it very insoluble in water, and harder to metabolize. Naphthalene-1,2-diol shows a higher Caco-2 permeability than naphthalene at 1.686, meaning it has a high level of absorption when administered or ingested orally and its intestinal absorption in humans is very high at 91.245%, meaning most of it is absorbed by the intestine. Naphthalene-1,2-diol shows a relatively high skin permeability with log Kp (-2.711), and a person runs a risk of dermal penetration from naphthalene-1,2-diol. Naphthalene-1,2-diol is not a P-glycoprotein substrate, meaning P-glycoprotein cannot bind to it to keep it from entering into the cell. However, naphthalene-1,2-diol does not also inhibit the mediated transport of compounds by any of the P-glycoproteins (I and II). Also, the results show that 2-methylnaphthalene (2-MN) has a molecular weight of 142.201 g/mol. It has a high log P value of 3.14822 indicating that it demonstrates an even higher affinity for the lipid phase than 2-MN. This means that 2-MN will be slowly metabolized and will be readily absorbed by the body of the patient. Its water solubility is very low with a value of -3.934, making it very insoluble in water, and harder to pass out of the body. 2-MN shows a high Caco-2 permeability at 1.527, meaning it has a high level of absorption when administered or ingested orally and its intestinal absorption in humans is very high at 95.257%. 2-MN shows a Skin Permeability of (-1.597) log Kp, meaning it has relatively low penetration through the skin, and a person is not really at risk of dermal penetration from 2-MN. 2-MN is a P-glycoprotein substrate, meaning P-glycoprotein can bind to it to keep it from entering into the cell. Hence, 2-MN does not inhibit the mediated transport of compounds by any of the P-glycoproteins (I and II). However, 1-methylnaphthalene (1-MN) has a molecular weight of 142.201 g/mol. It has a high affinity for the lipid phase with a logP value of 3.14822. This means that 1-MN will be slowly metabolized and will be readily absorbed by the body of the patient. Its water solubility is low at (-4.006), making it very insoluble in water, and harder to pass out of the system. 1-MN shows a high Caco-2 permeability at 1.476., meaning it has a high level of absorption when administered or ingested orally

and its intestinal absorption in humans is very high at 96.813%. 1-MN shows a Skin Permeability (log Kp) of (-1.535), meaning it has relatively low penetration through the skin, and a person is not really at risk of dermal penetration from 1-MN. 1-MN is a P-glycoprotein substrate, meaning P-glycoprotein can bind to it to keep it from entering into the cell. Also, 1-MN does not inhibit the mediated transport of compounds by any of the P-glycoproteins (I and II). Naphthalene-1,2,6,7-tetrol has a molecular weight of 192.17 g/mol. It has a logP value of 2.8398, meaning it is lipophilic. This implies that naphthalene-1,2,6,7-tetrol will be slowly metabolized and will be readily absorbed by the body of the patient. Its water solubility value is very low at (-3.037). Naphthalene-1,2,6,7-tetrol shows a high Caco-2 permeability at 0.567, meaning it has a low level of absorption when administered or ingested orally and its intestinal absorption in humans is very high at 94.422%. Naphthalene-1,2,6,7-tetrol shows a Skin Permeability of (-2.735) log Kp, meaning it has a high penetration through the skin, and a person runs a risk of dermal penetration from naphthalene-1,2,6,7-tetrol. Naphthalene-1,2,6,7-tetrol is a P-glycoprotein substrate, meaning P-glycoprotein can bind to it to keep it from entering into the cell. Hence, naphthalene-1,2,6,7-tetrol does not inhibit the mediated transport of compounds by any of the P-glycoproteins (I and II).

Table 1
Physicochemical and Absorption properties

Property	Naphthalene	Naphthalene-1,2-diol	2-MN	1-MN	Naphthalene-1,2,6,7-tetrol
Molecular Weight	128.174	160.172	142.201	142.201	192.17
LogP	2.8398	2.251	3.14822	3.14822	1.6622
Water solubility (log mol/L)	-3.496	-2.449	-3.934	-4.006	-3.037
Caco-2 permeability (log Papp in 10^{-6} cm/s)	1.574	1.686	1.527	1.476	0.567
Intestinal absorption (human) %	95.157	91.245	95.257	96.813	94.422
Skin Permeability (log Kp)	-1.433	-2.711	-1.594	-1.535	-2.735
P-glycoprotein substrate	Yes	No	Yes	Yes	Yes
P-glycoprotein I inhibitor	No	No	No	No	No
P-glycoprotein II inhibitor	No	No	No	No	No

Distribution Properties of Naphthalene and its Derivatives

Naphthalene has a high volume of distribution (0.488), meaning it would be highly distributed in other tissues rather than plasma. After binding to several biomolecules in the human body, a relatively little fraction of naphthalene remains unbound and in a free state in the body. It has been predicted to have 0.144 (14.4%) of its ingested volume unbound. Naphthalene has a Blood-Brain Barrier (BBB) permeability (log BB) value of 0.434, which means that it readily crosses the BBB, and is well distributed to the brain.

Its Central Nervous System (CNS) permeability (log PS) value of -1.254 also indicates that it can penetrate the CNS. Naphthalene-1,2-diol has a high VDss (0.258), meaning it would be highly distributed in other tissues rather than plasma. After binding to several biomolecules in the human body, a relatively little fraction of naphthalene-1,2-diol, though higher than naphthalene remains unbound and in a free state in the body. It has been predicted to have 0.272 (27.2%) of its ingested volume unbound. Naphthalene-1,2-diol has a Blood-Brain Barrier (BBB) permeability (log BB) value of 0.537, which means that it readily crosses the BBB, even more readily than naphthalene and is well distributed to the brain. The Central Nervous System (CNS) permeability (log PS) value of -1.773 also indicates that it can penetrate the CNS. 2-MN has a very high VDss value (0.586). This means it would be highly distributed in other tissues rather than in the blood plasma. A relatively little fraction of 2-MN remains unbound and in a free state in the body. It has been predicted to have 0.144 (14.4%) of its ingested volume unbound. 2-MN has a Blood-Brain Barrier (BBB) permeability (log BB) value of 0.455, which means that it readily crosses the BBB, and is well distributed to the brain. Its Central Nervous System (CNS) permeability (log PS) value of -1.358 also indicates that it can penetrate the CNS.

1-MN has a high VDss value of 0.488, indicating it would be highly distributed in other tissues rather than plasma, and a higher dose would be required to attain uniform concentration with the plasma. A relatively little fraction of 1-MN remains unbound. About 0.132 of the original ingested volume remains unbound and free in the body. 1-MN has a Blood-Brain Barrier (BBB) permeability (log BB) value of 0.481, which means that it readily crosses the BBB, and is well distributed to the brain. Its Central Nervous System (CNS) permeability (log PS) value of -1.388 also indicates that it can penetrate the CNS.

Naphthalene-1,2,6,7-tetrol has the highest VDss value amongst the derivatives listed (1.169), meaning it would have the highest distribution in other tissues rather than plasma. However, close to half of the ingested volume remains unbound (0.452). Naphthalene-1,2,6,7-tetrol has a Blood-Brain Barrier (BBB) permeability (log BB) value of (-1.001), making it poorly distributed to the brain. Its Central Nervous System (CNS) permeability (log PS) value of -2.262 also indicates that it has low but, possible penetration in the CNS.

Table 2
Distribution Properties of Naphthalene and its Derivatives

Property	Naphthalene	Naphthalene-1,2-diol	2-MN	1-MN	Naphthalene-1,2,6,7-tetrol
VDss (human) (log L/kg)	0.488	0.258	0.586	0.728	1.169
Fraction unbound (human) (Fu)	0.144	0.272	0.114	0.132	0.452
BBB permeability (log BB)	0.434	0.537	0.455	0.481	-1.001
CNS permeability (log PS)	-1.254	-1.773	-1.358	-1.388	-2.262

Metabolic Profile (Cytochrome P450 promiscuity) of Naphthalene and its Derivatives

From the results in Table 4.3, CYP2D6 and CYP3A4 do not metabolize naphthalene or any of its derivatives. CYP1A2 is inhibited by naphthalene and its derivatives. However, CYP2C9 and CYP2C19 activity are inhibited by only 2-methylnaphthalene and 1-methylnaphthalene, while naphthalene and its derivatives show no inhibitory effect on CYP2D6 and CYP3A4.

Table 3
Metabolism: Human Cytochrome-P450 promiscuity

Property	Naphthalene	Naphthalene-1,2-diol	2-MN	1-MN	Naphthalene-1,2,6,7-tetrol
CYP2D6 substrate	No	No	No	No	No
CYP3A4 substrate	No	No	No	No	No
CYP1A2 inhibitor	Yes	Yes	Yes	Yes	Yes
CYP2C19 inhibitor	No	No	Yes	Yes	No
CYP2C9 inhibitor	No	No	Yes	Yes	No
CYP2D6 inhibitor	No	No	No	No	No
CYP3A4 inhibitor	No	No	No	No	No

Excretion and Clearance Properties of Naphthalene and its Derivatives

Naphthalene a has a low level of total clearance (hepatic and renal clearance), with a Total Clearance (log ml/min/kg) value of just 0.198, meaning it will not be easily excreted from the body. Also, naphthalene is not a substrate of the Renal Organic Cation Transporter 2 (OCT2) protein. This means that the kidney will play little or no part in the excretion of naphthalene. Naphthalene-1,2-diol a has a low level of total clearance (hepatic and renal clearance), with a Total Clearance (log ml/min/kg) value of just 0.154, meaning it will not be easily excreted from the body. Also, naphthalene-1,2-diol is not a substrate of the Renal Organic Cation Transporter 2 (OCT2) protein. This means that the kidney will play little or no part in the excretion of naphthalene-1,2-diol. Furthermore, 2-methylnaphthalene has a fairly-higher of total clearance (hepatic and renal clearance), with a Total Clearance (log ml/min/kg) value of just 0.213, meaning it will not be easily excreted from the body. Also, naphthalene is not a substrate of the Renal Organic Cation Transporter 2 (OCT2) protein. This means that the kidney will play little or no part in the excretion of naphthalene. 1-MN has a low level of total clearance, with a Total Clearance (log ml/min/kg) value of just 0.221, making it the highest amongst the discussed naphthalene derivatives. However, it still will not be easily excreted from the body. Also, 1-MN is not a substrate of the Renal Organic Cation Transporter 2 (OCT2) protein. This means that the kidney will play little or no part in the excretion of naphthalene. Naphthalene-1,2,6,7-tetrol has the lowest level of total clearance amongst the discussed naphthalene derivatives, with a Total Clearance (log ml/min/kg) value of just 0.026, meaning it is hardly

ever passed out of the body. Also, naphthalene-1,2,6,7-tetrol is not a substrate of the Renal Organic Cation Transporter 2 (OCT2) protein. This means that the kidney will play little or no part in the excretion of naphthalene-1,2,6,7-tetrol.

Table 4
Excretion and Clearance Properties of Naphthalene and its Derivatives

Property	Naphthalene	Naphthalene-1,2-diol	2-MN	1-MN	Naphthalene-1,2,6,7-tetrol
Total Clearance (log ml/min/kg)	0.198	0.154	0.213	0.221	0.026
Renal OCT2 substrate	No	No	No	No	No

Toxicological Properties of Naphthalene and its Derivatives

Naphthalene is not mutagenic, and will not act as a carcinogen. The maximum tolerated dose (log mg/kg/day) in humans is 0.703, making the human body able withstand a fairly-high daily naphthalene intake. Naphthalene does not inhibit the potassium (K^+) channels encoded by the hERG genes I and II. Also, exposure to naphthalene at a concentration of 1.942 mol/kg proved lethal to 50% of the rats being tested. Before then, adverse effects were already observed on exposure to 0.8522 mol/kg (antilog of LOAEL value). Naphthalene has no resulting hepatotoxicity and is not implicated in liver dysfunction. Though, it causes skin sensitization and may be responsible for allergic reactions on exposure. At a *T. pyriformis* toxicity (log µg/L) level of 0.584 which is toxic, naphthalene exposure inhibited the growth of over 50% of the *T. pyriformis* worked with, and at a Minnow toxicity (log mM) level of 0.52, naphthalene exposure killed over 50% of the minnows under exposure., making it not so toxic to the Minnows. Naphthalene-1,2-diol is not mutagenic, and will not act as a carcinogen. The maximum tolerated dose (log mg/kg/day) in humans is 0.514, making the human body able to withstand a fairly-high daily naphthalene-1,2-diol intake. Naphthalene-1,2-diol does not inhibit the potassium (K+) channels encoded by the hERG genes I and II. Exposure to naphthalene-1,2-diol at a concentration of 2.009 mol/kg proved lethal to 50% of the rats being tested. Before then, adverse effects were already observed on exposure to 0.7105 mol/kg (antilog of LOAEL value). Naphthalene-1,2-diol has no resulting hepatotoxicity and is not implicated in liver dysfunction. Though, it causes skin sensitization and may be responsible for allergic reactions on exposure. At a *T. pyriformis* toxicity (log µg/L) level of 0.815 which is toxic, naphthalene-1,2-diol exposure inhibited the growth of over 50% of the *T. pyriformis* worked with, and at a minnow toxicity (log mM) level of 1.023, naphthalene-1,2-diol exposure killed over 50% of the minnows under exposure., making it even less toxic than naphthalene to the Minnows. 2-Methylnapthelene is not mutagenic, and will not act as a carcinogen. The maximum tolerated dose (log mg/kg/day) in humans is 0.62, making the human body able to withstand a fairly-high daily 2-MN intake. 2-MN does not inhibit the potassium (K^+) channels encoded by the hERG genes I and II. Moreover, exposure to 2-MN at a concentration of 1.953 mol/kg proved lethal to 50% of the rats being tested. Before then, adverse effects were already observed on exposure to 0.8407 mol/kg (antilog of LOAEL value). 2-MN has no resulting direct hepatotoxicity and is not implicated directly in liver dysfunction. Though, it causes skin sensitization and

may be responsible for allergic reactions on exposure. At a *T. pyriformis* toxicity (log µg/L) level of 0.833 which is toxic, 2-MN exposure inhibited the growth of over 50% of the *T. pyriformis* worked with, and at a Minnow toxicity (log mM) level of 0.343, 2-MN exposure killed over 50% of the minnows underexposure., making it not so toxic to the Minnows. 1-Methylnaphthalene (1-MN) is not mutagenic, and will not act as a carcinogen. The maximum tolerated dose (log mg/kg/day) in humans is 0.609, making the human body able to withstand a fairly-high daily 1-MN intake. 1-MN does not inhibit the potassium (K+) channels encoded by the hERG genes I and II. Exposure to 1-MN at a concentration of 1.942 mol/kg proved lethal to 50% of the rats being tested. Before then, adverse effects were already observed on exposure to 0.8489 mol/kg (antilog of LOAEL value). 1-MN has no resulting hepatotoxicity and is not implicated in liver dysfunction. Though, it causes skin sensitization and may be responsible for allergic reactions on exposure. At a *T. pyriformis* toxicity (log µg/L) level of 0.846 which is toxic, 1-MN exposure inhibited the growth of over 50% of the *T. pyriformis* worked with, and at a Minnow toxicity (log mM) level of -0.145, 1-MN exposure killed over 50% of the minnows underexposure., making it very toxic to the minnows. Naphthalene-1,2,6,7-tetrol is not mutagenic, and will not act as a carcinogen. The maximum tolerated dose (log mg/kg/day) in humans is 0.385, making the resistance of the human body to naphthalene-1,2,6,7-tetrol very low, meaning even small amounts can prove toxic to humans. Naphthalene-1,2,6,7-tetrol does not inhibit the potassium (K^+) channels encoded by the hERG genes I and II. Exposure to naphthalene-1,2,6,7-tetrol at a concentration of 2.499 mol/kg proved lethal to 50% of the rats being tested. Before then, adverse effects were already observed on exposure to 0.3653 mol/kg (antilog of LOAEL value) mol/kg. Naphthalene-1,2,6,7-tetrol has no resulting hepatotoxicity nor skin sensitization and ergo is not implicated in liver dysfunction or allergic skin reaction of any kind. At a non-toxic level of *T. pyriformis* toxicity (log µg/L) − 0.327, naphthalene-1,2,6,7-tetrol exposure inhibited the growth of over 50% of the *T. pyriformis* worked with, and at a minnow toxicity (log mM) level of 2.268, naphthalene-1,2,6,7-tetrol exposure killed over 50% of the minnows under exposure., making it barely toxic at all to the minnows.

Table 5
Toxicological Properties of Naphthalene and its Derivatives

Property	Naphthalene	Naphthalene-1,2-diol	2-MN	1- MN	Naphthalene-1,2,6,7-tetrol
AMES toxicity	No	No	No	No	No
MTD (human) (log mg/kg/day)	0.703	0.514	0.62	0.609	0.385
hERG I inhibitor	No	No	No	No	No
hERG II inhibitor	No	No	No	No	No
ORAT (LD50) (mol/kg)	1.942	2.099	1.953	1.962	2.499
ORCT (LOAEL) (log mg/kg_bw/day)	2.345	2.035	2.318	2.337	1.441
Hepatotoxicity	No	No	No	No	No
Skin Sensitisation	Yes	Yes	Yes	Yes	No
T. pyriformis toxicity (log ug/L)	0.584	0.815	0.833	0.846	0.327
Minnow toxicity (log mM)	0.52	1.023	0.343	-0.145	2.268
MTD = Maximum Tolerated Dose; ORAT = Oral Rat Acute Toxicity; ORCT = Oral Rat Chronic Toxicity; LOAEL = Lowest Observed Adverse Effect Level					

Endocrine Disruption Potential of Naphthalene and Selected Derivatives

Most times, naphthalene and its derivatives act as EDCs in the body disrupting the activities of endocrine system leading to adverse health outcomes such as alterations in sperm quality and fertility, abnormalities in sex organs, endometriosis, early puberty, altered nervous system function, immune function, certain cancers, respiratory problems and so many more (Gridan et al., 2019). The results show how likely naphthalene and its derivatives are to disrupt certain hormone processes that are responsible for homeostasis in the human body

Table 6
Prediction of the endocrine disruption potential of naphthalene and selected naphthalene derivatives.

Receptor	Naphthalene	Naphthalene-1,2-diol	2-MN	1-MN	Naphthalene-1,2,6,7-tetrol
Androgen receptor	-6.8	-7.3	-7.1	-7	-7.4
Androgen receptor an	-6.7	-7.1	-7.4	-7	-7.2
Ooestrogen receptor α	-6.2	-6.8	-6.7	-6.9	-6.9
Ooestrogen receptor α an	-6.6	-7.1	-6.9	-7	-7
Ooestrogen receptor β	-6.4	-6.9	-7.1	-7	-7
Ooestrogen receptor β an	-6.5	-6.7	-6.8	-7	-6.9
Glucocorticoid receptor	-6.1	-6.6	-6.7	-6.8	-6.8
Glucocorticoid receptor an	-6.2	-6.7	-6.8	-6.8	-6.5
Liver X receptor α	-6.9	-7.7	-7.6	-7.6	-7.6
Liver X receptor β	-7.4	-7.5	-7.9	-8	-7.7
Mineralocorticoid receptor	-6.4	-6.9	-6.9	-6.8	-7.2
Peroxisome proliferator-activated receptor α	-6.2	-6.5	-6.7	-6.4	-6.6
Peroxisome proliferator-activated receptor β	-6.9	-7	-7.4	-7.5	-7
Peroxisome proliferator-activated receptor γ	-6.9	-6.5	-7.5	-6.6	-6.7
Progesterone receptor	-2.5	-2.7	-2.5	-2.5	-2.5
Retinoid X receptor α	-6.5	-6.7	-7.2	-6.9	-6.7
Thyroid hormone receptor α	-7.1	-7.7	-7.7	-7.8	-7
Thyroid hormone receptor β	-6.7	-7.2	-7.4	-7.3	-6.9

Discussion

ADME-Tox properties

This study was conducted to evaluate the risk value of the pharmacokinetic and toxicological endpoint properties of naphthalene and its derivatives, and also to evaluate the most basic human implication which is the disruption of the hormonal system. The results from the study performed shows that all except naphthalene-1,2-diol are substrates of P-glycoprotein, meaning they can be transported out of the cell by the P-glycoprotein. Also, they do not inhibit the transporter action of either of the protein subtypes

(I and II), meaning they do not affect the exfiltration of other compounds from the cell. From the distribution properties derived from the conducted study, all except naphthalene-1,2,6,7-tetrol permeate the Blood-Brain Barrier very readily, making them well distributed to the brain. This in turn will most likely lead to neurological complications in the brain and possible brain damage. The CYP1A2 enzyme is localized to the Endoplasmic Reticulum (ER), and functions to metabolize Polyunsaturated Fatty Acids (PUFAs) into signalling molecules. It plays the monooxygenase role of metabolizing arachidonic acid into 19-hydroxyeicosatetraenoic acid (19-HETE). The study carried out showed that CYP1A2 is inhibited by naphthalene and all the examined derivatives, making them a possible culprit in several cases involving inflammation, hypertension, and a possible cause of metastatic growth in the human breast and prostate cancer. CYP2C19 is another important enzyme in the CYP450 family although it is only inhibited by 2-MN and 1-MN. CYP2C19 metabolizes over 10% of commonly prescribed drugs and plays an active role in the synthesis of cholesterol, steroids, and other lipids. The activity of 2-MN and 1-MN causes CYP2C19 to be inhibited, causing certain drugs to accumulate in the liver cells, and in rare cases, leading to hepatoxicity, and liver damage. CYP2C9 is the primary enzyme for metabolizing nonsteroidal anti-inflammatory drugs, oral antidiabetic agents, and angiotensin II receptor blockers, and also in the disposition of warfarin. The interference of CYP2C9 by 2-MN and 1-MN is likely to cause accumulation of the drugs in the plasma and make these drugs to perform their said functions in the body.

Endocrine disruption potential

The predictive study on the endocrine disruption showed the selected compounds have a high affinity for the androgen receptor. Androgen is a steroid hormone that is associated with the development and maintenance of male characteristics in vertebrates by binding to androgen receptors (Zhou 2010). Androgen is also present however in females, but in lower amounts, and they act as precursors to oestrogens in both men and women. Androgen disruption has been linked with so many cases of cancer in the reproductive tract, especially testicular and prostate cancers. This implies that in the long run, naphthalene and its derivatives can be responsible for the aforementioned disorders in the reproductive system. Our results show that Naphthalene-1,2,6,7-tetrol has the highest affinity for the androgen receptor, meaning it has the greatest potential for androgen function disruption. Oestrogens are steroid hormones secreted by the ovaries and function as female sex hormones. They play a key role in the growth and overall development of females and are responsible for the development of secondary female characteristics such as breast enlargement, and fertility. However, the results from the study carried out shows that the discussed compounds have a great affinity for oestrogen receptors, meaning they will bind easily to these receptors and hinder oestrogen activity. Oestrogen receptor disruption due to phthalates (such as naphthalene and its derivatives) is the cause of some disorders in females, such as impaired fertility or infertility, shortened lactation, endometriosis (when the tissue that lines the inside of the uterus grows outside the uterus to other parts of the body) (Carin and Janssen, 2008). Oestrogen disruption from naphthalene and its fellow phthalates also increase the risk of menstrual irregularities and a disease condition known as Polycystic Ovarian Syndrome whose symptoms include irregular periods, pelvic pain, and ovarian cysts. Even males aren’t entirely safe as naphthalene also affects the development of males from exposure in the womb. We can conclude that is responsible for certain

disorders such as hypospadias (a birth defect of the penis), cryptorchidism (undescended testicles), and even impaired fertility from reduced sperm count and semen quality, and in some cases testicular and prostate cancer. Corticosteroid receptors, which include Glucocorticoid receptors (GR) and Mineralocorticoid receptors (MR), are widely expressed in humans and are involved in many diseases and health outcomes. GR and MR mediate the actions of glucocorticoids and mineralocorticoids, respectively, which are involved in many physiological processes including metabolism and immune response by anti-inflammation (Odermatt and Gumy, 2008; Kadmiel and Cidlowski, 2013). Naphthalene and its derivatives have shown to have a great affinity for corticosteroid receptors. Dysregulations in glucocorticoid activities have been linked to birth defects, mood and cognitive disorders, cancer, immune disease, allergic disease, metabolic dysfunction, and cardiovascular disease (Carnahan and Goldstein, 2000; Odermatt and Gumy, 2008). These discussed compounds disrupt glucocorticoid and mineralocorticoid activity by altering GR/MR transactivation (Zhang *et al.*, 2016). The liver X receptor is a member of the nuclear receptor family of transcription factors and is closely related to nuclear receptors such as PPARs, FXR, and RXR (retinoid receptors) are critical for lipid signalling and membrane homeostasis, and their dysfunction has been implicated in metabolic disorders such as hyperlipidemia, diabetes mellitus, atherosclerosis and cancer (Wang and Tontonoz 2018). The naphthalene-induced disruption of this hormone's functions leads to degeneration of liver cells, high level of cholesterol, and impaired liver function. The progesterone hormone is often referred to as the 'pregnancy hormone'. From the research carried out, progesterone receptor activity shows very little potential for disruption by naphthalene or either of the discussed derivatives. However, in a situation where naphthalene-induced progesterone disruption occurs, naphthalene causes the progesterone to lose its ability to drop the mother's immunity to allow for pregnancy, causing fetal death. The retinoic acid receptors, which include two distinct families, the RARs and RXRs are nuclear receptors that function either as homodimers or as heterodimers with other receptors such as peroxisome proliferator-activated receptors (PPARs; NR1C1–3), liver X receptors (LXRs; NR1H2–3), or farnesoid X receptor (FXR; NR1H4), and others (Masaki and Hiroki, 2018). They function as nuclear receptors with roles in development, cell differentiation, metabolism, and death. Their inhibition by naphthalene and its derivatives from chronic exposure at concentrations equal to hundreds of nanograms a litre or more can cause a wide variety of dysmorphogenesis (formation of abnormal tissues) in various tissues (e.g., eye, brain, limb and body axis) of fish, amphibians, birds, and mammals.The thyroid receptors are home to two major hormones produced by the thyroid gland: triiodothyronine and thyroxine. Compounds that disrupt thyroid activity (naphthalene and its derivatives included) do so by affecting the hypothalamo-pituitary-thyroid axis or directly via thyroid hormone receptors (Murthy and Murthy, 2012). The implications of thyroid disruption from naphthalene and its derivatives vary with the phase of development of the host and the role of the thyroid hormones during that period. Exposure to thyroid disruptors such as naphthalene and its derivatives in a pregnant woman and early years of life will lead to neurodevelopmental problems leading to low IQ scores, possible cognitive and behavioural defects, and possible deafness in such children (Korrick and Sagiv, 2008). In adults, this disruption will cause thyroid autoimmune disorders, thyroid neoplasms, hypothyroidism, and cardiovascular risk due to altered lipid metabolism, with 2-MN and 1-MN having the highest disruption potential.

Conclusion

Based on the outcome of the study carried out, naphthalene has proven to be toxic in humans. Naphthalene and its derivatives have also been proven to disrupt endocrine activity and hormonal balance in the body. This in turn could be the reason for several naphthalene-induced endocrine disruptions and diseases. Further experimental studies are recommended to investigate the predictive toxicological effects of naphthalene and its derivatives on endocrine function.

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