INTEGRATION OF SAFETY AND HEALTH ASSESSMENT IN FORMULATED PRODUCT DESIGN FRAMEWORK

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ABSTRACT

Consumers are commonly exposed to numerous chemical ingredients found in various formulated products that may cause safety and health hazards. Presently, there are limited systematic tools are presented to assess the safety and health effects of the chemical ingredients in formulated products. Therefore, the safety and health assessment of ingredients contained in products should be performed in the early stage of product design. This is to avoid the need to redesign the products at the final stage. This research purposed the integration of safety and health assessment in formulated product design framework. Firstly, the design of formulated product ingredients with the integration of safety and health aspects by the computer-aided molecular design (CAMD) technique is presented. In CAMD, a set of target properties are identified in terms of molecular physical and thermodynamic properties to ensure that the designed molecules can achieve the product functionalities. In this thesis, the aspects of safety and health are emphasised by considering them as design objectives in CAMD technique along with the product functionalities. Secondly, an index-based safety and health assessment known as product ingredient safety and health index (PISHI) was proposed to estimate the severity of the hazards of ingredient candidates. New inherent safety and health sub-indexes were introduced to improve the established safety and health hazards needed in formulated product design. Basically, the inherent safety and health sub-indexes are assigned with a score, based on the degree of the potential hazards. A higher score refers to the higher safety and health hazards, and vice versa. The basic toxicology information of the ingredients is required in PISHI. Thirdly, another safety and health assessment was proposed known as product ingredient exposure index (PIEI) to estimate the extent of risks of the ingredient candidates via dermal and inhalation exposure routes. Four case studies on formulated products including paint, detergent, sunscreen and eye cream are presented. The design of formulated product ingredients for paint formulation shows that the solvent mixtures candidates possess adequate short evaporation time with low content of volatile organic compound to reduce the health effects. The applicability of the PISHI and the PIEI in the formulated product design framework is presented in the new design of detergent formulation. The high hazards ingredient candidates in detergent formulation were eliminated based on the scores from PISHI and PIEI. Furthermore, the applicability of the PISHI and the PIEI in identifying the high hazard and risk chemical ingredients has was validated using the existing sunscreen formulation. The chemical ingredient in the sunscreen formulation, vitamin A received high hazard score and was eliminated by the PISHI. This is in agreement with the banning of vitamin A in sunscreen products by European union. Finally, the screening of ingredient candidates by the PISHI and the PIEI was proven by experimental testing where ingredients in the design of eye cream formulation showed good product performance and simultaneously possessed low safety and health risks. The safety and health assessment was integrated into the formulated product design framework, hence, contributing as systematic decision-making tool. This proposed assessment ensures that all ingredient candidates are the ones that have the desirable properties and simultaneously reduce the potential safety and health hazards to consumer.

ABSTRAK

Pengguna biasanya terdedah kepada bahan kimia yang terdapat dalam pelbagai produk yang boleh menyebabkan bahaya keselamatan dan kesihatan. Pada ketika ini, kaedah sistematik untuk menilai kesan keselamatan dan kesihatan bahan kimia dalam produk adalah terhad. Oleh itu, penilaian keselamatan dan kesihatan bahan kimia harus dilakukan pada peringkat awal reka bentuk produk. Ini untuk mengelak keperluan sesuatu produk direka semula pada peringkat akhir. Penyelidikan ini bertujuan untuk menyatukan penilaian keselamatan dan kesihatan dalam kerangka reka bentuk produk yang dirumuskan. Pertama, reka bentuk ramuan produk yang diformulasikan dengan penyatuan aspek keselamatan dan kesihatan dengan teknik reka bentuk molekul dengan bantuan komputer (CAMD) ditunjukkan. Dalam CAMD, satu set sifat – sifat sasaran telah dikenal pasti dari aspek sifat fizikal dan termodinamik molekul untuk memastikan molekul yang direka mencapai fungsi yang dikehendaki dalam sesuatu produk. Dalam tesis ini, aspek keselamatan dan kesihatan ditekankan dengan menjadikannya sebagai objektif dalam reka bentuk teknik CAMD. Kedua, penilaian keselamatan dan kesihatan berdasarkan indeks dicadangkan yang dikenali sebagai indeks keselamatan dan kesihatan bahan produk (PISHI) untuk menganggar tahap bahaya calon ramuan. Sub-indeks keselamatan dan kesihatan inheren yang baharu telah diperkenalkan untuk menilai bahaya keselamatan dan kesihatan yang diperlukan dalam reka bentuk produk yang dirumuskan. Pada asasnya, setiap sub-indeks keselamatan dan kesihatan diberi skor, berdasarkan tahap bahaya. Skor yang lebih tinggi merujuk kepada bahaya keselamatan dan kesihatan yang lebih tinggi, dan sebaliknya. Ketiga, satu lagi penilaian keselamatan dan kesihatan dicadangkan yang dikenali sebagai indeks pendedahan bahan produk (PIEI) untuk menganggar risiko pendedahan bahan kimia melalui hidung dan kulit. Empat kajian kes telah dibuat terhadap produk yang dirumuskan termasuk cat, pencuci, pelindung matahari dan krim mata. Reka bentuk bahan produk yang dirumuskan untuk formulasi cat telah menunjukkan bahawa calon campuran pelarut mempunyai masa penyejatan yang cukup singkat dengan kandungan sebatian organik mudah meruap yang rendah untuk mengurangkan kesan kesihatan. Kebolehgunaan PISHI dan PIEI dalam kerangka reka bentuk produk ditunjukkan dalam reka bentuk formulasi pencuci yang baharu. Calon bahan kimia yang berisiko tinggi telah disaring untuk formulasi pencuci berdasarkan skor dari PISHI dan PIEI. Selanjutnya, kebolehgunaan PISHI dan PIEI dalam mengenal pasti bahan kimia yang berisiko tinggi telah disahkan menggunakan formulasi pelindung matahari yang sedia ada. Untuk bahan kimia yang terdapat dalam formulasi, vitamin A mendapat skor bahaya tinggi dan telah disingkirkan oleh PISHI. Ini bersesuaian dengan larangan vitamin A dalam produk pelindung matahari oleh kesatuan Eropah. Akhirnya, penilaian calon bahan kimia oleh PISHI dan PIEI telah dibuktikan dengan kajian eksperimen bahawa ramuan dalam reka bentuk krim mata menunjukkan prestasi produk yang baik dan mempunyai risiko keselamatan dan kesihatan yang rendah. Penyatuan penilaian keselamatan dan kesihatan dalam kerangka reka bentuk produk yang dirumuskan telah menyumbang sebagai kaedah membuat keputusan yang sistematik. Penilaian keselamatan dan kesihatan yang dicadangkan ini memastikan bahawa semua bahan kimia yang disaring memberikan sifat yang diinginkan dan sekaligus mengurangkan potensi bahaya keselamatan dan kesihatan kepada pengguna.

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LIST OF ABBREVIATIONS

ACGIH - American Conference of Governmental Industrial Hygienists

AMG - Alkyl methyl glucamide

AOP - Adverse-Outcome-Pathway

ATSDR - Agency for Toxic Substances and Disease Registry (U.S.)

BAE - Branched alkyl ethoxylate

BAS - Branched alkylbenzene sulphonates

BAT - Biological tolerance value

BAuA - Federal Institute for Occupational Safety and Health in German

BEI - Biological exposure indices

BLEVE - Boiling Liquid Expanding Vapor Explosion

BTEX - Benzene, toluene, ethylbenzene and xylene

BMD - Benchmark dose

BP - Butylparaben

CAA - Chemical Alternatives Assessment

CalEPA - California Environmental Protection Agency

CAMD - Computer Aided Molecular Design

CARC - Carcinogenic

CEI - Chemical Exposure Index

CEL - Critical Exposure Limit

CLP - Classification, Labeling and Packaging of Chemical Products

CMC - Critical Micelle Concentration

CMR - Carcinogenicity, mutagenicity and reproductive toxicity

CompTox - Computational toxicology

COSHH - Control of Substance Hazardous to Health

COSMO - Conductor-like screening model

CompTox - Computational toxicology

COSHH - Control of Substance Hazardous to Health

COSMO - Conductor-like screening model

CEL - Critical Exposure Limit

COSMORS	-	Conductor-like screening model for real solvent
CP	-	Cloud point
CPD	-	Chemical Product Design
CSB	-	US Chemical Safety and Hazard Investigation Board
CSDS	-	Chemical safety data sheets
CTD	-	Chemical toxicity distributions
DDT	-	Dichlorodiphenyltrichloroethane
DEET	-	N, N-diethyl-3-methylbenzamide
DEGEE	-	Diethylene glycol monoethyl ether
DEP	-	Diethyl phthalate
DFG	-	Occupational Health and Safety in Deutsche Forschungsgemeinschaft
DNA	-	Deoxyribonucleic acid
DNEL	-	Derived no-effect level
ECHA	-	European Chemicals Agency
EDC	-	Endocrine-Disrupting Chemical
EFSA	-	European Food Safety Authority
EPA	-	Environmental Protection Agency
EP	-	Ethylparaben Propylparaben
EU	-	European Union
EU EPHECT	-	Emissions, Exposure Patterns and Health Effects of Consumer Products
EU REACH	-	European Union Registration, Evaluation, Authorisation and Restriction of Chemicals
EWG	-	Environmental Working Group
FDA	-	Food and Drug Administration
GAIA	-	Global Aquatic Ingredient Assessment
GCM	-	Diethylene glycol monoethyl ether
GPD	-	Group contribution method
GHS	-	Globally Harmonised System of Classification and Labelling Chemicals
GRAND	-	Graphical and Numerical Descriptive
HB	-	Hydrogen Bonding
HIRA	-	Hazard Identification and Ranking

HQ	-	Hydroquinone
HQI	-	Health Quotient Index
HSDB	-	Hazardous Substances Data Bank
HSE	-	The United Kingdom Health and Safety Executive
HTS	-	High Throughput Screening
HYSYS	-	HYprotech SYStems
IARC	-	International Agency for Research on Cancer
ICAS	-	Integrated Computer Aided System
IFA	-	Institute for Occupational Safety and Health of the German Social Accident Insurance
IFCET	-	Inherent Fire Consequence Estimation Tool
ILSI	-	International Life Science Institute
INRS	-	Institut National de Recherche et de Sécurité in French
IOHI	-	Inherent Occupational Health Index
IPEN	-	The International POPs Elimination Network
IPPC	-	Integrated Pollution Prevention and Control
IRET	-	Integrated Risk Estimation Tool
ISAPEDS	-	Inherent safety assessment technique for preliminary design stage
ISI	-	Inherent Safety Index
ISPI	-	Inherent Safety Performance Indices
i-TTC	-	Internal threshold toxicology concern
I2SI	-	Integrated Inherent Safety Index
IUPAC	-	International Union of Pure and Applied Chemistry
KIFS	-	Knowledge based ingredient formulation system
LAS	-	Linear alkyl benzene sulfonate
LC_{50}	-	Lethal concentration at which causes the death of 50% of a group of test animals
LCA	-	Life cycle assessment
LD_{50}	-	Lethal dosage at which causes the death of 50% of a group of test animals
LEL	-	Lower Exposure Limit
LFL	-	Lower Flammability Limit
LOAEL	-	Low observed adverse effect level
m-PIIS	-	Modified Prototype Index Inherent Safety

MAK	-	Maximum workplace concentration of chemical substance
MDTCC	-	Ministry of Domestic Trade, Co-operatives and Consumerism
MEC	-	Minimum Explosive Dust Concentration
MES	-	Methyl ester sulphonate
MILP	-	Mixed-integer linear Programming
MINLP	-	Mixed-integer Nonlinear Programming
MOE	-	Margin of exposure
MOIE	-	Margin of internal exposure
MOS	-	Margin of safety
MP	-	Methylparaben
MSDS	-	Material Safety Data Sheet
NF	-	Normal Fluid
NESIL	-	No expected sensitizing induction level
NFPA	-	National Fire Protection Association
NICNAS	-	National Industrial Chemicals Notification and Assessment Scheme
NIOSH	-	The United States National Institute for Occupational Safety and Health
NIST	-	National Institute of Standards and Technology
NOAEC	-	No observed adverse effect concentration
NOAEL	-	No observed-adverse- effect-level
NOEL	-	No observed effect level
NTP	-	National Toxicology Program U.S. Department of Health and Human Services
NuDIST	-	Numerical Descriptive Inherent Safety technique
OECD	-	Organization for Economic Co-operation and Development
OEHHA	-	Office of Environmental Health Hazard Assessment
ODP	-	Ozone-Depletion Potential
OEL	-	Occupational Exposure Limit
OHHI	-	Occupational Health Hazard Index
OHI	-	Occupational Health Index
OSHA	-	Occupational Safety and Health Administration
O/W	-	Oil-in-Water

PAS	-	Polar Associating
PBT	-	Persistence, bioaccumulation and toxicity
PCB	-	Polychlorinated Biphenyl
PCPs	-	Personal care products
PEL	-	Permissible Exposure Limit
PHAs	-	Poly(3-hydroxylalkonoates)
PHB	-	Polyhydroxybutyrate
PiF	-	Product Intake Fraction
PIIS	-	Prototype Index Inherent Safety
PISHI	-	Product Ingredient Safety and Health Index
PIEI	-	Product Ingredient Exposure Index
PNA	-	Polar Non-Associating
POD	-	Point of departure
POP	-	Persistent Organic Pollutants
PRHI	-	Process Route Healthiness Index
PRI	-	Process Route Index
PSI	-	Process Stream Index
QRA	-	Quantitative risk assessment
RCR	-	Risk characterization ratio
REACH	-	Registration, Evaluation, Authorization and Restriction of Chemical
RIVM	-	Dutch National Institute for Public Health and the Environment
R&D	-	Research and Development
R-phrase	-	Risk Phrases
SCCS	-	Scientific Committee on Consumer Safety
SCCP	-	Scientific Committee on Consumer Products
SCCNFP	-	Scientific Committee on Cosmetic Products and Non-Food Products
SCOEL	-	Scientific Committee on Occupational Exposure Limits
SDS	-	Sodium dioctyl sulfosuccinate
SED	-	Systemic exposure dose
SEN	-	Sensitization
SER	-	Social and Economic Council of the Netherlands
SIDS	-	Screening Information Dataset

SK	-	Skin
SLES	-	Sodium Lauryl Ether Sulfate
SPF	-	Sun protection factor
SVHC	-	Substance of very high concern
SVOC	-	Semi Volatile Organic Compound
TiO_2	-	Titanium dioxide
TLV	-	Threshold Limit Value
TMS	-	Thermomorphic solvent system
TNT	-	Trinitrotoluene
TORCAT	-	Toxic Release Consequence Analysis Tool
ToxCast	-	EPA's Toxicity Forecaster
TPD	-	Tangent Plane Distance
TTC	-	Threshold toxicology concern
UEL	-	Upper Exposure Limit
UFL	-	Upper Flammability Limit
UK	-	Upper Flammability Limit
USD	-	United States Dollar
USEPA	-	United States Environmental Protection Agency
UV	-	Ultraviolet
VOC	-	Volatile Organic Compound
WHO	-	World Health Organization
WoE	-	Weight-of-evidence
W/O	-	Water-In-Oil

LIST OF SYMBOLS

A	-	Amount per use
A_{LD50}	-	Universal constant for the GC model of LD_{50}
B_{LD50}	-	Universal constant for the GC model of LD_{50}
BW	-	Human body weights
CA	-	Contact area
C_{exp}	-	Exposure concentration
$C_{exp,d}$	-	Exposure concentration through dermal
$C_{exp,i}$	-	Exposure concentration through inhalation
C_i	-	Contribution of first-order group of type-i
C_{ing}	-	Concentration of ingredients
C_o	-	Oxygen stoichiometric coefficient
D_{abs}	-	Dermal absorption of the substance
D_j	-	Contribution of second-order group of type-j
E_k	-	Contribution of the third-order group of type-k
E_x	-	Explosiveness
F	-	Frequency of application of the substance
F_p	-	Flash point
F_{p0}	-	Universal constant for the GC model of F_p
FT	-	Film thickness
G_T	-	Total number of groups needed to form the molecules
g	-	Coefficient to represent the type (acyclic, monocyclic, bicyclic or tricyclic) of compounds
K	-	Number of data range
K_{ow}	-	Octanol / water partition coefficient
K_{ow0}	-	Universal constant for the GC model of octanol / water partition coefficient
K_{st}	-	Deflagration index
N	-	Ventilation rate
Pa. s	-	Pascal per second
P^{sat}	-	Vapor pressure

PR	-	Product retained
ppm	-	Part per million
T_b	-	Boiling point
T_{b0}	-	Universal constant for the GC model of T_b
T_m	-	Melting point
T_{m0}	-	Universal constant for the GC model of T_m
T_g	-	Glass transition temperature
W	-	Range width
n	-	Number of data
ºC	-	Degree celcius
ρ	-	Density
λ	-	Degree of satisfaction
δ	-	Solubility parameter
η	-	Viscosity
η^*	-	Universal constant for the GC model of viscosity
ΔG^{mix}	-	Gibbs energy of mixing
t	-	Shelf life
σ	-	Surface tension
s^{-1}	-	Per second
V	-	Volume of space
vol %	-	Percentage of volume
V_p	-	Target quality properties
λ_p	-	Degree of satisfaction of product quality properties
v_p^L	-	Lower bound of product quality properties
v_p^U	-	Upper bound of product quality properties
v_i	-	Valence of group *i*
M.Pa	-	Mega pascal
M_j	-	Frequency of second-order group of type-j
mv	-	Molar volume
Mw	-	Molecular weight (g/mol)
N_i	-	Frequency of first-order group of type-i
O_k	-	Frequency of third-order group of type-k

p	-	Property value
T^{90}	-	Evaporation time
R	-	Gas law constant
T	-	Temperature
x	-	Binary variable in general GC equation
z	-	Binary variable in general GC equation
λ_p	-	Degree of satisfaction for target property p
Ω_p	-	Property operator for target property p
δ_a	-	Solubility of additive
δ_b	-	Solubility of binder
δ_s	-	Solubility of solvent mixture
δ_{s0}	-	Universal constant for the GC model of solubility
δ_D	-	Hansen solubility dispersion
δ_P	-	Hansen solubility polar
δ_H	-	Hansen solubility H_2 bond
dB	-	Slope parameter
ζ_i	-	Variable of solvent *i* in the mixture
ζ	-	Variable of solvent mixture

LIST OF APPENDICES

CHAPTER 1

INTRODUCTION

1.1 Background of the Study

Chemical product design is gradually becoming a significant area of chemical engineering. Due to modern society needs, various chemical-based products have been manufactured rigorously (Zhang et al., 2017a). Chemical-based products can be classified into formulated products, molecular products, functional products, and devices (Gani & Ng, 2015). Formulated products are being widely used in daily life, for example, detergents, pesticides, pharmaceuticals, and personal care products (Zhang et al., 2017b). The ingredients present in formulated products may be of a variety of chemicals, namely pigments, solvents, polymers, surfactants, and odours. The mixing of these ingredients in a particular formulation will produce the desired product. However, some of the ingredients in the product have been found to contribute to safety and health hazards to consumers. The safety aspects of a product are those related to their properties of flammability, explosiveness, reactivity, toxicity, and corrosiveness. Controversial issues have arisen regarding some personal care products containing ingredients that are hazardous to health. For instance, phthalates contributed to endocrine-disrupting potential for pregnant women who used personal care products. Furthermore, children exposed to the ingredients in paint (e.g., lead) have resulted in neurobehavioral symptoms (Landrigan et al., 2018). Other health problems, such as neurotoxicity (Roy et al., 2017), respiratory difficulties (Mikes et al., 2019; Steinemann, 2017; Abd El Hamid Hassan et al., 2013), dermal irritation (Jongeneel et al., 2018; Schwen and Thyssen, 2016; Rodas et al., 2015; Matsumoto et al., 2016), and carcinogenicity (Rebelo et al., 2015; Matsumoto et al., 2016; Rodas et al., 2015) are the consequences of using formulated products. This indicates that the potential risk to human safety and health depends strongly on the ingredients in the finished products (Rebelo et al., 2015).

Not much work has been done to address the issues on the growing number of potentially toxic chemicals used as the ingredients in formulated products. Each day, numerous new chemical substances are introduced into the market with little or unknown facts of the potential risks. The typical approach on the formulated product design that has been practised so far has considered the aspects of product quality, manufacturing process (Bernardo & Saraiva, 2015; Wibowo & Ng, 2001; Fung et al., 2016; Gani & Ng, 2015; Zhang et al., 2017b), and economy (Fung et al., 2016; Gani & Ng, 2015). Nonetheless, some works have been done to consider the safety and health elements in new product design, for example, the works by Conte et al., (2010), Zhang et al., (2017b), and Ten et al., (2017). They developed a model-based system approach for integrated chemical product-process design. Consumer preferences are identified and arranged systematically before transforming them into the target properties. Another work by Ten et al., (2017) incorporated the safety and health aspects into the computer-aided molecular design (CAMD) method instead of other desirable properties. This approach ensures that the synthesised product does not contribute to the harmful condition and any health hazard to consumers. Most of the abovementioned works only included flammability and toxicity properties during the design of formulated products. Limited research has been done on estimating severe health hazards, such as carcinogenic and reproductive toxicity potential due to the exposure to chemical ingredients in formulated products.

It is the best approach to assess the safety and health aspects in formulated product design by employing the principle of inherent safety and health in process design. The basic concepts of inherent safety and health include intensification, substitution, attenuation, and simplification (Crowl & Louvar, 2011). The principle of intensification involves minimising the inventory of hazardous materials so that the exposure to these materials is reduced. The concept of substitution takes place when less harmful materials replace hazardous materials. The principle of attenuation promotes a milder and less hazardous condition of the chemical process. Meanwhile, simplification offers the elimination of unnecessary complexity in process design so that it is easy to comprehend. The most efficient way to apply this concept is at the early stages of the design phase. For a formulated product, the design stages based on the framework presented by Zhang et al., (2017b) as shown in Figure 1.1 begins with the identification of product attributes (Step 1), conversion of product attributes into the appropriate physicochemical properties (Step 2), determination of product form (Step 3), and generation of feasible ingredient candidates (Step 4). After the ingredient candidates have been selected, the composition of each ingredient in the formulation can be determined (Step 5). Next, the product quality is determined (Step 6) by two factors: the properties of the ingredients or mixtures and their product microstructure. All the target properties of the product are then verified by performing experiments (Step 7). If all the target properties are achieved, the final composition and product microstructure are determined and then, the process design can take place. Finally, the design of the manufacturing process is conducted, including the selection of several unit operations, such as mixing, heating, cooling, homogenisation, and filling.

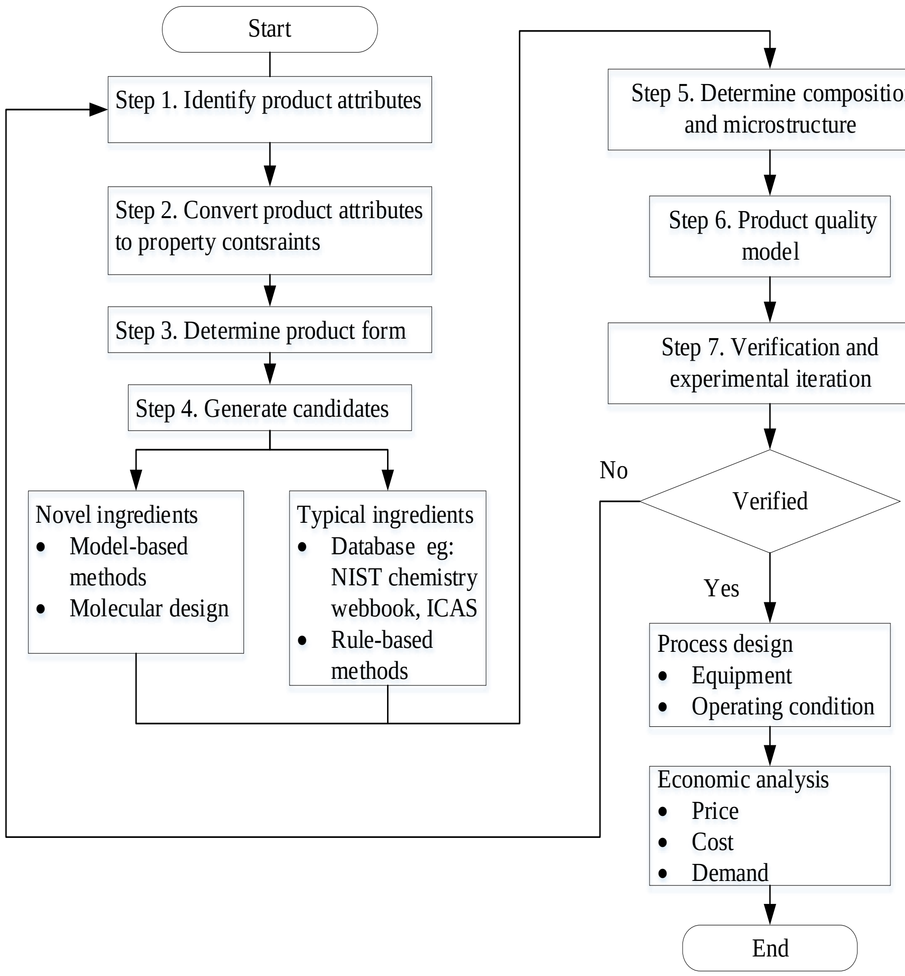

Figure 1.1 Formulated product design framework (Zhang et al., 2017b)

Based on the seven main steps discussed, the inherent safety and health concept can be applied during the early design stage, which is the generation of ingredient candidates (Step 4). The ingredient candidate can be either a novel ingredient that is not commercially available or a typical ingredient used in a formulated product that possesses low safety and health risks. The CAMD technique can be applied for the design of molecules so that the ingredient candidates possess desirable functionalities and may also consider the safety and health properties. Then, the ingredient candidates must undergo safety and health assessment to ensure that the selected ingredients are safe and less harmful to consumers. Hence, the idea of introducing the concept of inherent safety and health in the early stages of formulated product design has become the main objective of this research work.

Various methods are used to quantify and compare the level of inherent safety and health in process design. As the inherent safety and health assessment are well-established, they are suitable to be adopted into formulated product design. One of the most common safety and health assessment methods in process design is the index-based approach. Interestingly, the index-based approach delivers a fast and consistent outcome, which then helps in deciding the process synthesis route with better safety and health attributes (Gnoni & Bragatto, 2013). In process design, the design phase can be divided into several stages: the research and development (R&D) stage is for the selection of a chemical reaction pathway, the preliminary engineering stage where a process flow diagram is needed, and the basic engineering stage that requires a piping and instrumentation diagram. The examples of index-based approach for inherent safety assessment include the Prototype Index for Inherent Safety (PIIS) (Edwards and Lawrence, 1993), the Inherent Safety Index (ISI) (Heikkila, 1999), and the i-Safe (Palaniappan et al., 2002a; Palaniappan et al., 2002b). These methods help to evaluate the inherent safety level of a chemical process route according to several inherent safety parameters (e.g., flammability, explosiveness, and toxicity).

On the other hand, for the inherent occupational health, among the methods available for the assessment include the Inherent Occupational Health Index (IOHI) (Hassim & Hurme, 2010a), the Health Quotient Index (HQI) (Hassim & Hurme, 2010b), and the Occupational Health Index (OHI) (Hassim & Hurme, 2010c). The health parameters considered are the exposure limit, acute, and chronic effects. It should be noted that the selection of parameters is based on the availability of information during the design stages. The safety and health parameters can be categorised into two classes, namely the parameters for chemical substances, such as physical and chemical properties, and the parameters used for process conditions. At the early stage of formulated product design, which is during the generation of ingredient candidates (Step 4), only physical and chemical properties of the ingredient candidates can be obtained. Meanwhile, in process design, the safety and health index assessment for the R&D stage also require similar information, which is the basic information of chemical substances. Hence, the prominent safety and health index assessment in a chemical process for the R&D stage are identified and adopted in formulated product design. However, the parameters associated to process conditions are not applicable due to the unavailability of information. The process conditions of the product manufacturing are determined at the final stage of formulated product design as shown in Figure 1.1.

As mentioned previously, extensive works on formulated product design still lack on the safety and health aspects. Therefore, in this thesis, the concept of inherent safety and health is introduced into the formulated product design framework. The novelty of the thesis is presented with the improvement of the current formulated product design framework with the emphasis on safety and health aspects by three stages as shown in Figure 1.2. Firstly, the safety and health aspects are considered during the generation of ingredient candidates, either from the design of ingredients using CAMD or the selection from typical ingredient candidates available in databases. The optimisation model is applied in the CAMD technique to identify the chemical ingredients that satisfy consumer needs and simultaneously possess favourable safety and health attributes. Secondly, the safety and health assessment of the ingredient candidates is performed. The prominent index-based assessment in process design that is applicable to formulated product design is adopted. New inherent safety and health sub-indexes are introduced to improve the current safety and health hazards that are required in formulated product design.

The development of Product Ingredient Safety and Health Index (PISHI) is proposed to identify the potential safety and adverse health effects of the ingredient candidates. The level of severity of potential hazards with relevant exposure routes is estimated. Then, the development of Product Ingredient Exposure Index (PIEI) is used for the characterisation of risk based on the severity level of exposure. To further illustrate the proposed assessment, four case studies of the formulated products are presented.

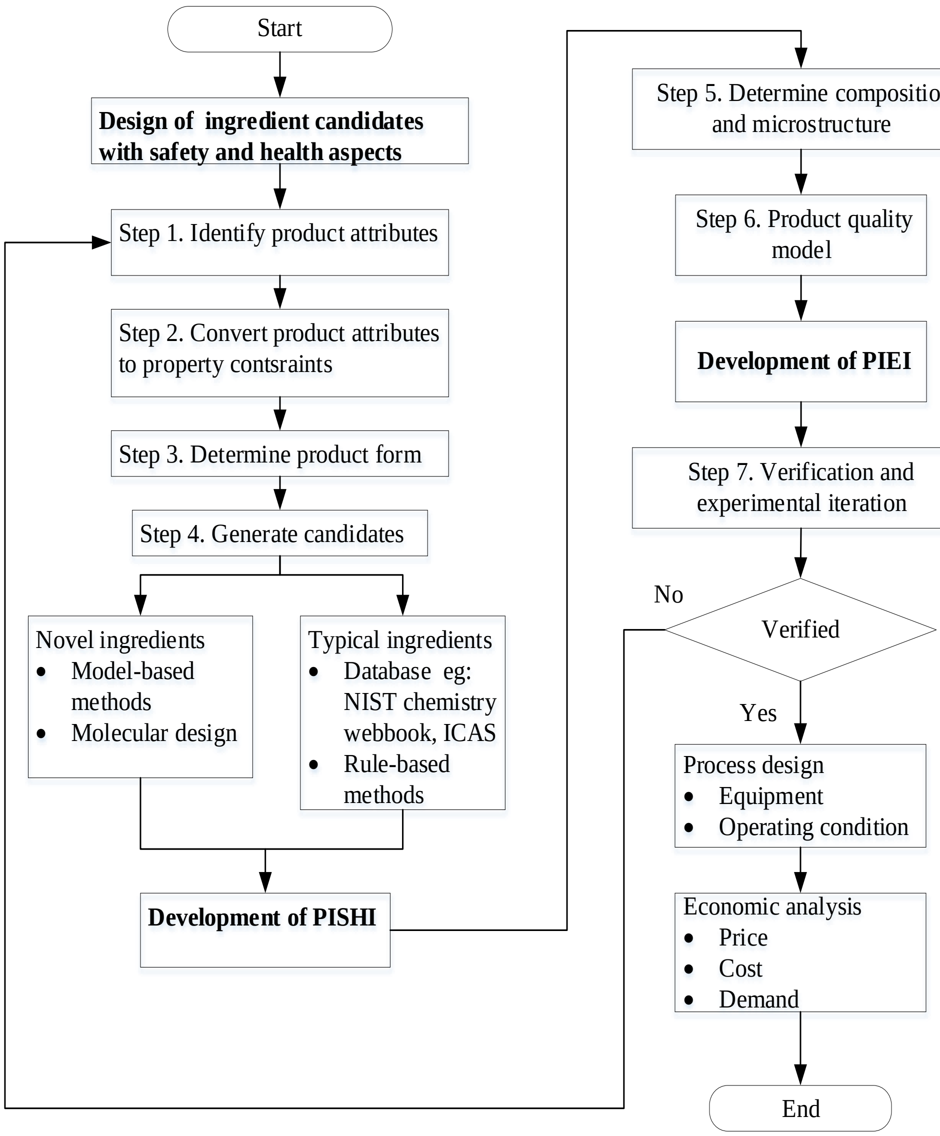

Figure 1.2 The integration of safety and health assessment in formulated product design framework

The case studies of formulated product design including paint, detergent, sunscreen and eye cream are chosen based on the significant safety and health issues found from the literatures. For example, the issue on majority of paint in Malaysia contain high lead level despite its severe health impacts to the consumer (CAP, 2016). In addition, each case study of formulated product has different product attributes, product form and classes of chemicals, such as pigment, solvent and surfactant as ingredients. Paint needs pigments as the active ingredient to provide colour for surface coating. Meanwhile, surfactant acts as an active ingredient for detergent to remove dirt from the surface being cleaned. The formulated products also differ in exposure scenarios, such as the amount per use and the frequency of use. The different case studies are chosen to prove that the PISHI and the PIEI are able to address the issues of hazardous ingredients. Furthermore, the application of the PISHI and the PIEI is flexible and suitable to be used despite the varieties of ingredients used in formulated product. The case studies are presented to show the applicability of the PISHI and the PIEI in the identification of the ingredients with high hazards and risks and able to guide in the elimination of high hazards and risks ingredients. The new generation of ingredient candidates is demonstrated to replace the hazardous ingredients. The case study of sunscreen formulation validated the applicability of the PISHI and the PIEI in formulated product design framework. Then, the case study of eye cream formulation proved that the ingredient candidates showed good product performances and simultaneously possessed low safety and health risks by experimental testing.

1.2 Problem Statement

Safety and health effects due to the exposure to a formulated product is an important issue to be tackled. The safety and health potential of a product largely depends on the selection of ingredients and the manufacturing process involved (Rebelo et al., 2015). Some efforts have been made (e.g., replacing the harmful ingredient in a product); however, there is also a challenge to achieve the desired functionality and behaviour of the product simultaneously.

Besides, in some works, the ingredient used as the substitute is unsafe. Hence, the CAMD technique can be employed to synthesise molecules as the ingredient candidates that achieve the specified target functionality properties and also display favourable safety and health performances.

Current CAMD works in formulated products have considered physicochemical properties as the main design criteria to fulfil the targeted product functionalities. However, these molecules that meet the functional properties may cause safety risks and adverse health effects. Limited CAMD works have considered the safety and health aspects during the design stage, where it is subjected to the availability of the property prediction model. More environmental-related property prediction models have been established by Hukkerikar et al., (2012a) in comparison to safety and health properties. Thus, the generated molecules by CAMD are mostly not optimised in terms of safety and health aspects. The available property prediction models with the aspects of safety and health include the flash point to determine flammability potential, the lethal dosage (LD_{50}), and the permissible exposure limit (PEL) to represent the health effect.

A conventional formulated product design framework only emphasises the product functionality performances to meet consumer needs. The aspect of safety is considered by following the safety regulations for the product to be in the market. For instance, cosmetic products in Malaysia must follow the Guidelines for Control of Cosmetic Products. The safety assessment for human health of the finished product, its ingredients, chemical structure, and level of exposure is included in Annex 1, part 12 in the guideline of the product information file. Thus, current safety assessment focuses more on assessing the safety and health hazards of a finished product rather than estimating them during the early stages of product design.

The safety and health risks of consumer exposure to ingredients in a product can be evaluated in two ways. The margin of exposure (MOE) is one of the approaches that can be applied to estimate the extent of the risks from the ingredients in the formulation. The value of MOE may also indicate the level of concern of the chemical ingredients and may contribute to the decision for risk management action (Benford et al., 2010). On the other hand, the Registration, Evaluation, Authorization, and Restriction of Chemical (REACH) regulation used the risk characterisation ratio (RCR) value to predict the potential human health risks. The ratio is calculated by comparing the value of derived no-effect levels (DNELs) to the estimated exposure levels. If the value of RCR is less than 1, the risk is considered safe (McKee et al., 2018). However, most of the works presented have applied two safety and health risk indicators on the finished product. The safety and health risk of the ingredients in a product should be estimated during the design stage. Hence, it is proposed that the safety and health assessment should be integrated into the formulated product design framework. The gaps identified in the current formulated product design are as follows.

In most of the previous works to design molecules used as the ingredients in a product, only certain safety and health properties are considered, such as flammability and environmental toxicity, apart from the product functional properties (Conte et al., 2010; Karunanithi et al., 2006; Mattei et al., 2014; Patel et al., 2010; Ten et al., 2017; Zhang et al., 2017b). The generated molecules by CAMD can either be novel ingredients or typical ingredients available in the market. If the generated molecules are novel ingredients, the properties of the molecules are based on the available related safety and health property prediction models. Meanwhile, for typical ingredients, other important safety and health properties, such as explosiveness, reactivity, chronic effects, and carcinogenicity can be obtained from physicochemical properties and toxicology databases. There is a major research gap to introduce the concept of inherent safety and health during the early design stages of formulated products. The generated molecules have not been optimised previously with the aspects of safety and health. The safety and health aspects should be considered as the design constraint in the CAMD technique to screen out hazardous molecules. Furthermore, another research gap is the safety and health properties of ingredient candidates have not been addressed previously, including explosiveness, reactivity, chronic effects, and carcinogenicity. Early consideration of a safer and less harmful chemical ingredient at the early design stages may reduce the risk of process safety hazards, such as fire, explosion, and toxicity during the product manufacturing stage. Numerous accidents have occurred in manufacturing industries and resulted in fatality, disability, or property damage, which can be avoided if no or less hazardous materials are handled. Conventionally, safety and health assessment are conducted at the final stage of product design, which is on the finished product. Generally, the assessment of the finished product is conducted to determine if the exposure of ingredients in a product exceeds the threshold. There is a research gap where the ingredient candidates should be assessed in the safety and health aspects at the early design stages to identify the potential hazards. Furthermore, to date, there is a lack of systematic methodology in the formulated product design framework that may serve as a decision-making tool for the selection of chemical ingredients. As the inherent safety and health index-based assessment have been established in process design, there is another research gap, which is to identify the applicability of the method in the formulated product design framework. It is proposed that the index-based assessment in process design can be applied in the formulated product design framework to fill this research gap.

1.3 Research Objectives

The main objective of this study is to introduce the concept of inherent safety and health into the formulated product design framework. The safety and health aspects are emphasised during the early design stages of a formulated product. Based on the research background and problem statement, the objectives of this study are:

(a) To design formulated product ingredients with the integration of safety and health aspects by the CAMD technique.
(b) To develop a safety and health hazard assessment on the formulated product ingredients.
(c) To develop a risk characterisation on the product ingredient exposure.

1.4 Scope of Study

In order to fulfil the objectives of the study, the scope of the study has been drawn as follows.

1.4.1 Design of Formulated Product Ingredients with the Integration of Safety and Health Aspects by CAMD Technique

The formulated product ingredients are designed using the CAMD technique by considering:

i. The safety and health aspects are considered in Step 1 in the formulated product design framework, which is the identification of product attributes.
ii. The product functionality, safety, and health properties are chosen as the design objectives.
iii. The target properties are commonly estimated through group contribution-based property prediction models.
iv. The optimised molecules are assessed using PISHI and PIEI to identify the potential hazards and the severity of risk exposure.

1.4.2 Development of Safety and Health Hazard Assessment on Formulated Product Ingredients

An index-based assessment is proposed to assess the safety and health hazards of the formulated product ingredients including:

i. The development of safety and health hazard assessment is known as PISHI that can be performed after the generation of ingredient candidates in the formulated product design framework.
ii. The pioneer in index-based assessment employed in chemical process design is adopted.

iii. New inherent safety and health sub-indexes are developed based on the safety and health effects from the exposure of the formulated products.
iv. The inherent safety sub-indexes presented include explosiveness, flammability, and chemical reactivity.
v. The inherent health sub-indexes are arranged based on the exposure routes of eye, inhalation, dermal, and ingestion.
vi. The new sub-indexes of severe health hazards due to the toxicology endpoints of mutagenicity, reproductive toxicity, carcinogenicity, and endocrine-disrupting potential are developed.
vii. The safety and health levels of ingredient candidates are determined based on the allocation of score indicating the low, medium, and high hazard.

1.4.3 Development of Risk Characterisation on Product Ingredient Exposure

The risk characterisation is used to estimate the human health risk of exposure to formulated product ingredients. This assessment includes:

i. The development of risk characterisation is known as the PIEI that can be conducted after the determination of product quality model in the formulated product design framework.
ii. The determination whether the exposure of ingredients in a product exceeds the threshold.
iii. The allocation of scores is performed to classify the magnitude of risk of either low, medium, or high.
iv. The consideration of the two primary exposure routes of formulated products, namely dermal contact and inhalation.

1.5 Significance of the Study

This research introduces the concept of inherent safety and health at the early design stages of the formulated product design framework. The early consideration of the inherent safety and health concepts may significantly reduce the risk of redesigning the products at the final stage. The current formulated product design framework has been improved with the emphasis on safety and health aspects at the following design stages (shown in Figure 1.2): i) At the first stage, the design of the formulated product ingredient candidates has considered the safety and health aspects as the design objectives, ii) At the fourth stage, the novel index-based assessment of PISHI is presented to assess the safety and health hazards of ingredient candidates and iii) At the sixth stage, the novel index-based assessment of PIEI is used to assess the safety and health risks of ingredient candidates. The allocation of scores in PISHI and PIEI can reveal the severity level of hazard and risk. With the scores, hazardous ingredients can be identified and avoided in product formulation. A novel systematic safety and health assessment provides a swift and straightforward approach to search for alternative ingredients to eliminate or reduce the potential safety and health hazards of the synthesised product. Indeed, the decision-making concerning safety and health aspects in formulated product design will be easier and faster with this method.

1.6 Thesis Outline

The outline of this thesis is organised as follows. Chapter 2 presents the literature review of the formulated product design framework, CAMD and its application, the concept of safety and health, and existing safety and health approaches in formulated product design. Meanwhile, the discussion on the principles of inherent safety and health in chemical process and the adoption of the principles into formulated product design are presented.

Chapter 3 covers the methodology of the three proposed research objectives. The methodology begins with integration of safety and health assessment in formulated product design framework. Then, the design of formulated product ingredients with the aspects of safety and health by CAMD technique is presented. The application of the safety and health assessment, the PISHI and the PIEI are also presented. Four case studies of paint, detergent, sunscreen and eye cream formulation are then demonstrated in Chapters 4 to 7 respectively.

The first case study considers the design of new solvent-based paint as presented in Chapter 4. The inherent safety concept is introduced in the design of the solvent mixtures with the consideration of evaporation time and the presence of VOC. The application of PISHI to identify the high hazard ingredients is presented with two scenarios: the high hazard ingredients are eliminated at the early stage of product design and the high hazard ingredients are considered in the design.

The second case study covers the design of new detergent formulation, as presented in Chapter 5. The safety and health effects due to the exposure to preservatives and non-ionic surfactants are the main concern and need to be considered during the design of the ingredient candidates. The elimination of high risk ingredients based on the application of the PISHI and the PIEI is shown. The new generation of ingredient candidates for substitution is demonstrated.

The third case study presented in Chapter 6 is on the design of sunscreen formulation. The sunscreen formulation from the literature is presented to validate the application of the PISHI and the PIEI to screen the highly hazardous ingredient in the formulation.

The fourth case study presents the design of new eye cream formulation. The application of the PISHI and the PIEI has used to select the safer and less harmful ingredient candidates in the eye cream formulation. Then, the eye cream formulation has been prepared and tested in the laboratory to verify the product functionality performances, safety and health effects.

1.7 Summary

Formulated product design is a comprehensive approach in product development. Some of the ingredients used in formulated products are reported to contribute to safety and health hazards to consumers. Exposure to some of the formulated products may cause respiratory difficulties and skin irritation, and some have even been identified as carcinogenic to human. The safety and health aspects have not been thoroughly included in most of the formulated product design frameworks. Therefore, in this thesis, the current formulated product design framework developed by Zhang et al., (2017b) has been improved with the emphasis on safety and health aspects. The first objective of this thesis is to design the formulated product ingredients by considering the safety and health aspects. The chemical ingredient candidates generated by the CAMD technique are optimised in terms of product functionality performances, and safety and health aspects. The next objective is to develop a novel systematic safety and health assessment on the chemical ingredients. It comprises hazard identification as the second objective (i.e., the development of PISHI) and risk characterisation as the third objective (i.e., the development of PIEI) to be integrated into the formulated product design framework. Based on the result of the PISHI and the PIEI, the hazardous ingredients are screened out; thus, safer and less harmful ingredients are identified. The novel systematic safety and health assessment may ease the ingredient selection process. In addition, the current formulated product design framework has been improved with the emphasis on safety and health aspects. Finally, the potential safety risk and adverse health effects from the product usage can be reduced or eliminated.

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LIST OF PUBLICATIONS

Indexed Journal with Impact Factor

1. **Rafeqah Raslan**, Mimi H. Hassim, Nishanth Gopalakrishnan Chemmangattuvalappil, Denny K. S. Ng., Joon Yoon Ten. (2020). Safety and health risk assessment methodology of dermal and inhalation exposure to formulated products ingredients. *Regulatory, toxicology and Pharmacology.* 116, pp. 104753. https://doi.org/10.1016/j.yrtph.2020.104753. **(Q1, cite score: 5.8)**

2. **Rafeqah Raslan**, Mimi H. Hassim, Nishanth Gopalakrishnan Chemmangattuvalappil, Denny K. S. Ng., Joon Yoon Ten. (2020). Development of inherent safety and health index for formulated product design. *Journal of Loss Prevention and Process Industries.* 66. https://doi.org/10.1016/j.jlp.2020.104209. **(Q1, cite score: 5.3)**

3. **Rafeqah Raslan**, Mimi H. Hassim, Nishanth Gopalakrishnan Chemmangattuvalappil, Denny K. S. Ng., Joon Yoon Ten. Design of household products ingredients with minimum safety and health risk. (2020). *Pertanika Journal of Science and Technology*. 28 (S1):137-149. **(Q3, cite score: 0.7)**

4. Teck H. Soh, Mimi H. Hassim, **Rafeqah Raslan**, Nishanth G. Chemmangattuvalappil, Joon Y. Ten, Wai S. Ho. Wai S. Ho, Umi A. Asli, Mohd J. Kamaruddin. A Novel Surfactant Molecular Design with Optimal Performance, Safety and Health Aspects for Laundry Detergent. (2021). *Chemical Engineering Transaction.* 83: 517-522. https://doi.org/10.3303/CET2183087. **(Q3, cite score: 1.3)**

Indexed Conference Proceedings

1. **Raslan, R.**, M.H. Hassim, D.K.S. Ng, N.G. C., and N. Norafneeza, Safety and Health Index Development for Formulated Product Design: Paint Formulation. E3S Web Conf., 2019. 90: p. 03002. https://doi.org/10.1051/e3sconf /20199003002. **(Indexed by SCOPUS)**

2. **Rafeqah Raslan**, Mimi H. Hassim, Nishanth Gopalakrishnan Chemmangattuvalappil, Denny K. S. Ng. A Novel Methodology for Health Hazard and Risk Assessment of Dermal and Inhalation Exposure. MATEC Web Conf., 2021. 333:10002. https://doi.org/10.1051/matecconf/202133310002. **(Indexed by WOS)**