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Design of Household Products Ingredients with Minimum Safety and Health Risk

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ABSTRACT

In household products, specific chemical ingredients are used to satisfy the desired target properties as required by the consumers. However, some of these ingredients may result in safety risks and adverse health effects. Early consideration of safety and health aspects during product design is vital to minimize the impact on consumers. Safety and health aspects have not been strongly emphasized before in many product design methodologies. Therefore, a systematic methodology is proposed to assess the safety and health effects of the potential ingredients, before they are used in the product formulation. The chemical ingredient candidate may be a novel ingredient or a typical ingredient used in formulated product design. In this work, a computer-aided molecular design (CAMD) technique was used to design the novel ingredient candidates with the integration of safety and health aspects. Then, the safety and health performance of the ingredient candidates were assessed by inherent safety and health sub-indexes. Each safety or health parameter was assigned with a score, based on the degree of the potential hazards. A higher score was given to the ingredients with higher safety risk or more severe health effect, and *vice versa*. The result of the safety and health assessment based on the

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score allocation had contributed to the selection of chemical ingredient. This new approach ensures that the selected ingredient possesses desirable properties as well as low safety and health effects. A case study on surfactant design is presented to illustrate the incorporation of safety and health aspects into product design methodologies.

Keywords: Health, household product design, optimization, risk, safety

INTRODUCTION

Household products are widely and regularly being used in daily activities for cleaning, refreshing, and bleaching. The increase of household chemical usage has resulted in health impact to the consumer. Children around five years old are suffering from respiratory tract irritation due to exposure to household chemicals (Mikes et al., 2019). Dermal exposure to household chemicals such as geraniol has led to skin sensitization (Jongeneel et al., 2018). Health risk assessment on hazardous ingredients contained in cleaning products has been performed for chloroxylenol (Yost et al., 2016), geraniol (Jongeneel et al., 2018) and isothiazolinones (Garcia-Hidalgo et al., 2018). Meanwhile, dermal and inhalation exposure assessments of deodorizing products have been conducted by Kim et al. (2018) and Lee et al. (2018). Current health risk assessments are more focused on assessing the household chemicals in a finished product rather than estimating the health impact during the early stage of product design. If hazardous chemicals can be identified during the early product design stage, it can be replaced with inherently safer chemicals. This type of safety concept is known as inherent safety, which was first introduced in the 1970s by Trevor Kletz (as cited in Srinivasan & Natarajan, 2012). The basic concept of inherent safety and health includes minimization, substitution, moderation and simplification (Crowl & Louvar, 2011). The adoption of inherent safety principles into product design can be made by avoiding the use of hazardous chemicals during product formulation design.

A computer-aided molecular design (CAMD) technique is identified to be a powerful tool to quickly generate and evaluate the vast number of molecules that possess certain desirable functional properties (Liu et al., 2019). It is noted that in most CAMD problems, the main design criteria are the molecular functionalities as represented by the physical and chemical properties. However, these molecules that meet the functional properties may cause safety risks and adverse health effects. Several works have been presented on a molecular design where safety and health properties have been integrated into CAMD. The integration of both safety and health properties into the CAMD framework is developed by assigning each property with a score based on the degree of potential hazards (Ten et al., 2016). The generated molecule with a higher score has a higher hazard level and vice versa. The aspect of safety has been included in designing solvent candidates to be used as bio-oil additives (Mah et al., 2019). CAMD has also been used to identify alternative solvents to extract residual oil from palm pressed fibre with the consideration of safety aspect

(Ooi et al., 2019). Limited CAMD works have been reported on the design of household products ingredients with safety and health aspects as target properties. Furthermore, the design of chemical candidates has incorporated limited aspects of safety and health as it is restricted to the availability of property prediction model. More environmental-related property models have been established by Hukkerikar et al. (2012a) in comparison to safety and health properties.

The safety and health aspects have not been emphasized before in many of CAMD problems, especially for household products. The design of novel chemical ingredients must be optimized not only in terms of functional properties but also their safety and health performance. In addition, there is a lack of a systematic safety and health assessments methodology that can be integrated during the early stage of product design. The safety and health performance of the generated molecule by CAMD (novel ingredient) and the typical ingredient used in product formulation must be assessed to ensure that the selected chemical ingredients meet the functional criteria as well as safe to consume. In this work, the safety and health properties are incorporated into CAMD technique coupling with safety and health assessments through an index-based methodology. This new approach has highlighted the safety and health aspects during the early stage of product design.

MATERIALS AND METHODS

Design of Novel Ingredients

The molecular design problem began with the identification of product functionality properties. These product functionality properties were matched in physical and chemical properties. Such properties are known as target properties (V_p), which must fall within the specified upper bounds (v_p^{U}) and lower bounds (v_p^{L}) to ensure that the molecules function and behave in the desired characteristics. This constraint is shown in Equation (1) following the CAMD approach.

$$v_p^{\mathrm{L}} \leq V_p \leq v_p^{\mathrm{U}} \qquad \forall p \in P \tag{1}$$

where p represents the target property and V_p is for target property value.

The target properties were then calculated through the property prediction models following the selected groups of building blocks. An established approach known as group contribution method (GCM) was used to estimate the target physical and chemical properties of a molecule. The target property can be estimated by summing up the frequency of each selected group in the molecule multiplied by its contribution (Marrero & Gani, 2001) as shown in Equation (2).

$$f(X) = \sum N_i C_i \tag{2}$$

where $f(X)$ is the function of the target property X, C_i is the contribution of the first-order group that occurs N_i times. The first-order groups comprise a large set of simple and basic molecular groups that cover a wide range of organic compounds including CH3, CH2, CH, CHO and OH.

In the optimization model, the single-objective optimization problem was solved where only one target property was selected as an objective function. The remaining target properties would act as property constraints to be fulfilled. The target properties and its GCM equation models are shown in Supplementary Table 1 in Appendix. The physical and chemical properties considered were molecular weight (M_w), melting point (T_m) and boiling point (T_b). The safety property is represented by the value of flammability which is based on the value of flashpoint, Fp and boiling point, T_b. Meanwhile, health properties including toxicity (LD_{50}) and permissible exposure limit (PEL) are considered. The property model of PEL represents the chronic type of toxicity from the dermal and inhalation route with the basis of 8 hours daily exposure time. The optimal molecules were then evaluated based on their safety and health performance by the application of product ingredient safety index (PISI). With this, only molecules that are inherently safer and healthier as well as meeting the desired target properties are selected for product formulation design.

Selection of Typical Ingredients

The selection of typical ingredients has been discussed by Zhang et al. (2017) where chemical ingredient databases and rule-based methods were applied. The chemical ingredient databases can be obtained from National Institute of Standards and Technology (NIST) Chemistry WebBook and Integrated Computer Aided System (ICAS) database. Besides, the rule-based methods have been used to select the chemical ingredient as presented in the design of inkjet ink (Tam et al., 2016) and cream and paste (Wibowo & Ng, 2001). However, not all the typical chemical ingredients possess the properties that are needed for the product. Therefore, a novel chemical ingredient can be designed.

Safety and Health Assessments by Applying Product Ingredient Safety Index (PISI)

The chemical ingredient candidates (novel and typical ingredients) are evaluated based on their safety and health performances by the application of Product Ingredient Safety Index (PISI). It is applied to estimate the potential hazards at the early stage of product design, which is after the generation of ingredient candidates. In PISI, a score is assigned to distinguish among the low, medium and high degree of safety and health effects of the ingredients. A higher number of score indicates a higher degree of the severity of the hazards and vice versa. The lowest score is "zero" to indicate that the ingredient does not affect the particular safety or health property. The score of 1 represents low safety and health effects and a score of 2 for medium effects. The high scores of 3 and 4 are assigned

to indicate the high degree of safety and health effects. In this work, it was proposed that ingredient with a low degree of effects (score of 2 and below) was selected for the design of product formulation.

There are seven sub-indexes presented in PISI including flammability, toxicity, PEL, eye, skin, inhalation and ingestion exposures. The existing inherent safety and health indexes are modified and applied to assess the level of severity of safety and health effects caused by the ingredient candidates. The scores assigned to the sub-indexes are shown in supplementary materials (Supplementary Table 2 to Supplementary Table 8). Flammability is based on the flashpoint and boiling point where it was assessed following the established rating system by the National Fire Protection Association (National Fire Protection Association, 2020). The acute oral toxicity, LD_{50} was assessed to estimate the potential of the chemical ingredient to cause acute health effect. Since the group contribution model for LD_{50} (acute oral toxicity) is available, it is included as toxicity sub-index. Meanwhile, the exposure limit is represented by the data on PEL for chronic type toxicity. Hazard classification developed by Globally Harmonised System of Classification and Labelling of Chemicals (United Nations, 2013) provides the hazard indication corresponding to the level of danger by using precautionary statements and hazard codes. The GHS classification of a chemical substance is available in material safety data sheets (MSDS), chemical safety data sheets (CSDS) and chemistry database provided by the National Institute of Health (NIH) via PubChem search engine. The allocation of scores for the eye, skin, inhalation and ingestion exposures are based on the severity level of the health hazard effects. The higher the severity of the effect, the higher the score is allocated. The workflow of the safety and health assessments of the novel and typical ingredients is shown in Figure 1.

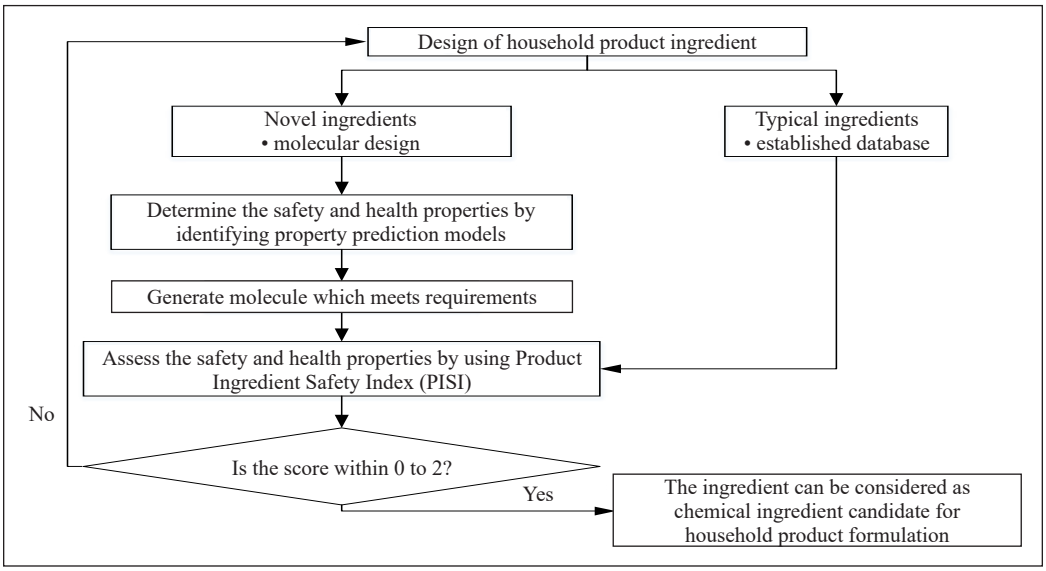


Figure 1. Work-flow diagram of household product ingredient design

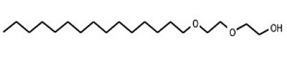
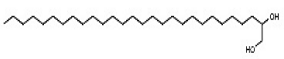
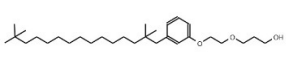
RESULTS AND DISCUSSION

The safety and health assessments by the application of PISI for two case studies on a novel and typical ingredients used in surfactant design are presented. Surfactant is an active ingredient used in household cleaning products. The surfactant must not only possess high cleaning performance but also able to protect the consumers' skin and has low toxicity (Mattei et al., 2013).

Design of Novel Ingredients

The novel ingredients were designed by selecting the following groups of molecular blocks such as CH_3, CH_2, CH, OH, CH_2O, aCO, aCH and aCC. The objective was to design a non-ionic surfactant with minimum toxicity potential. Hence, single-objective optimization was used in CAMD technique where acute oral toxicity, LD_{50} was chosen as an objective function. The optimal surfactant molecule was screened out and generated by CAMD. There were three non-ionic surfactants obtained, which were linear alkyl ethoxylate (surfactant 1), alkanediol (surfactant 2) and phenol ethoxylate (surfactant 3). The molecular structure and the target properties are shown in Table 1. All properties are determined using the property prediction model as shown in Supplementary Table 1.

Table 1
Properties of novel ingredients

Properties	Surfactant 1	Surfactant 2	Surfactant 3
Molecule	$C_{19}H_{40}O_3$	$C_{28}H_{58}O_2$	$C_{30}H_{54}O_3$
Molecular structure			
Mw (g/mol)	316.53	426.77	462.76
Fp (°C)	248.03	370.86	343.33
T_m (°C)	61.08	112.70	120.45
T_b (°C)	377.80	462.72	452.88
LD_{50} (mg/kg)	145.13	235.47	57.55
PEL (ppm)	6.04	5.16	0.12

The allocation of scores for the three generated surfactant molecules shown in Table 2 is based on the safety and health sub-indexes presented in PISI. All the molecules obtained a score of 1 for flammability sub-index indicating that the molecules possessed low flammability potential. Meanwhile, the three surfactant molecules also received a similar score of 2 for toxicity potential. For PEL, surfactant 3 received a high score of 4, indicating that it has a higher potential of health hazard in comparison to surfactant 1 and surfactant 2 that received a score of 3. However, all the novel surfactant molecules can

be considered as a highly hazardous ingredient concerning PEL. Thus, it can be decided that no generated surfactant molecule can be selected as the ingredient candidates for household product formulation.

Table 2
Scores of novel ingredients

Properties	Surfactant 1	Surfactant 2	Surfactant 3
Flammability	1	1	1
LD_{50}	2	2	2
PEL	3	3	4

Selection of Typical Ingredients

The typical ingredient candidates of surfactants are taken from the detergent formulation established by Zhang et al. (2017) and Seider et al. (2017). The physical and chemical properties of the typical ingredients including the flash point and boiling point are shown in Table 3. The health hazard potential is represented by referring to the hazard classification of four exposure routes of eye, skin, inhalation and ingestion (United Nations, 2013).

Table 3
Properties of typical ingredients

Properties	Alcohol ethoxylate	Alkyl N-methyl glucamide	Nonoxynol-9
Fp (°C)	77.2	110	197
T_b (°C)	225.6	300	250
LD_{50} (mg/kg)	2850	500	1400
PEL (ppm)	Not available	Not available	Not available
Eye	H318	H318	H319
Skin	No effect	No effect	H315
Inhalation	No effect	No effect	No effect
Ingestion	H302	No effect	H302

The scores of the typical surfactant candidates are given based on the safety and health sub-indexes in PISI as shown in Table 4. The alcohol ethoxylate obtained a high score of 3 for eye exposure hazard and score of 2 for flammability potential. For alkyl N-methyl glucamide, no high scores were obtained indicating a low safety and health hazard potential. Furthermore, nonoxynol-9 received a high score of 3 for eye exposure, while a score of 2 for skin exposure. According to Mattei et al. (2014), the usage of non-ionic surfactant is known to be much gentler on skin compared to other types of surfactant. However, nonoxynol-9 has the potential to cause skin irritation as shown by the hazard statement, H315 in Table 3. For alkyl N-methyl glucamide, the low score of 1 is received for flammability and score of 2 for eye exposure. As a whole, alcohol ethoxylate and nonoxynol-9 possessed a high

degree of severity of eye exposure. It is worth to note that alkyl N-methyl glucamide is found to be safer and healthier compared to the other two surfactant candidates since it only received scores of 2 and below. Hence, alkyl N-methyl glucamide can be considered as surfactant candidates in the product formulation.

Table 4
Scores of typical ingredients

Properties	Alcohol ethoxylate	Alkyl N-methyl glucamide	Nonoxynol-9
Fp	2	1	1
T_b	0	0	0
LD_{50}	0	2	1
Eye	3	2	3
Skin	0	0	2
Inhalation	0	0	0
Ingestion	1	0	1

The design of surfactant presented by Liu et al. (2019) and Seider et al. (2017) had highlighted the environmental toxicity where LC_{50} property was optimized. It is noted that the safety and health effects of the surfactant had not been considered. However, in this work, two steps of safety and health aspects had been taken into consideration. Firstly, the safety and health aspects had been incorporated into the product design. Secondly, the safety and health performance of the ingredient candidates was assessed by using PISI. The safety and health performance of the generated novel ingredients was assessed by considering its flammability, LD_{50} and PEL. Thus, the score assigned to the novel ingredient is referring to the sub-indexes presented in Supplementary Table 2, Supplementary Table 3 and Supplementary Table 4. The eye, skin, inhalation and ingestion sub-indexes are not applicable since no data on hazard classification by GHS are available for novel ingredients. On the other hand, the safety and health performance of the typical ingredient candidates can be assessed based on all sub-indexes presented in PISI because the safety and health properties required can be obtained. The ingredient with a low score (score of 2 and below) can be considered as safe and can be selected as feasible surfactant candidate for household product formulation.

CONCLUSION

The proposed methodology is capable of helping users on decision making to consider the selection of safer and healthier ingredient. Based on the result of the safety and health assessment by PISI, the ingredients with high safety and health hazard can be identified. Eliminating high safety risk and adverse health effects ingredients at the early stage of design may avoid changes made after the product is developed. Further study can be carried

out to take into account the concentration of the ingredients in the product formulation as it is decided during the later stages of product design. After the concentration of the ingredients has been decided, it is suggested that the ingredient candidates are to be analyzed further. For instance, a toxicology test might be considered during laboratory experiments to validate the proposed methodology. However, the safety and health assessment of the chemical ingredient by the application of PISI is sufficient as an initial tool to screen the highly hazardous ingredient.

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APPENDIX

Supplementary Table 1
List of target properties

Property	Group contribution method
Molecular weight, Mw (g/mol)	$\mathrm{Mw} = \sum_i N_i Mw_i$
Normal melting point, T_m (°C) (Hukkerikar et al., 2012b)	$\exp\left(\frac{T_m}{T_{mo}}\right) = \sum_i (N_i T_{mi})$ $T_{mo} = 143.5706\mathrm{K}$
Normal boiling point, T_b (°C) (Hukkerikar et al., 2012b)	$\exp\left(\frac{T_b}{T_{bo}}\right) = \sum_i (N_i T_{bi})$ $T_{bo} = 244.5165\mathrm{K}$
Flash point, F_p (°C) (Hukkerikar et al., 2012b)	$F_p - F_{po} = \sum_i (N_i F_{pi})$ F_{po}=170.7058K
Toxicity, LD_{50} (mol/kg) (Hukkerikar et al., 2012a)	$-\log LD_{50} - A_{LD50} - B_{LD50} M_w = \sum_i N_i LD_{50i}$ A_{LD50} =1.9372 B_{LD50} = 0.0016
Permissible exposure limit, PEL (mol/m^3) (Hukkerikar et al., 2012a)	$-\log(\mathrm{PEL}) = \sum_i N_i \mathrm{PEL}_i$

Supplementary Table 2
Flammability sub-index

Hazard indicator	Score information	Score
Flash point, (F_p) (National Fire Protection Association, 2020)	Non-flammable	0
	$F_p \geq 93.4$°C	1
	$F_p < 93.4$°C	2
	$F_p < 37.8$°C	3
	$F_p < 22.8$°C and $T_b < 37.8$°C	4

Supplementary Table 3
Toxicity sub-index

Hazard indicator	Score information	Score
Toxicity (LD_{50}) (mg/kg) (Heikkila, 1999)	$LD_{50} > 2000$	0
	$500 < LD_{50} \leq 2000$	1
	$50 < LD_{50} \leq 500$	2
	$5 < LD_{50} \leq 50$	3
	$LD_{50} \leq 5$	4

Supplementary Table 4
Exposure limit sub-index

Hazard indicator	Score information	Score
Permissable exposure limit (PEL) (Vapour, ppm) (Heikkila, 1999)	PEL > 1000	0
	PEL ≤ 1000	1
	PEL ≤ 100	2
	PEL ≤ 10	3
	PEL ≤ 1	4

Supplementary Table 5
Eye contact sub-index

Hazard indicator	Score information	Score
Acute effect (United Nations, 2013)	No effect	0
	H320: Cause eye irritation	1
	H319: Cause serious eye irritation	2
	H318: Cause serious eye damage	3

Supplementary Table 6
Skin exposure sub-index

Hazard indicator	Score information	Score
Acute effect (United Nations, 2013)	No effect	0
	H312: Harmful in contact with skin	1
	H311: Toxic in contact with skin	2
	H310: Fatal in contact with skin	3
Skin corrosion / irritation	H316: Cause mild skin irritation	1
	H315: Cause skin irritation	2
	H314: Cause severe skin burns	3
Skin sensitization	H317: May cause an allergic skin reaction	3

Supplementary Table 7
Inhalation exposure sub-index

Hazard indicator	Score information	Score
Acute effect (United Nations, 2013)	No effect	0
	H332: Harmful if inhaled	1
	H331: Toxic if inhaled	2
	H330: Fatal if inhaled	3
Respiratory irritation	H335: May cause respiratory irritation	2
Respiratory sensitization	H334: May cause allergy or asthma symptoms or breathing difficulties if inhaled	3

Supplementary Table 8
Ingestion exposure sub-index

Hazard indicator	Score information	Score
Acute effect (United Nations, 2013)	No effect	0
	H302: Harmful if swallowed	1
	H301: Toxic if swallowed	2
	H300: Fatal if swallowed H304: May be fatal if swallowed and enter airways	3