Pharm Res (2015) 32:1105–1127
DOI 10.1007/s11095-014-1523-z

RESEARCH PAPER

Safety Risk Categorization of Organic Extractables Associated with Polymers used in Packaging, Delivery and Manufacturing Systems for Parenteral Drug Products

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Received: 16 July 2014 / Accepted: 12 September 2014 / Published online: 4 October 2014

ABSTRACT

Purpose To develop and justify a Risk Evaluation Matrix for estimating the safety risk associated with extractables from plastic materials used in pharmaceutical applications and to apply that matrix to approximately 510 extractables to assess the risk that they would accumulate in drug products at levels sufficiently high to affect patient safety.

Method The Risk Evaluation Matrix considers toxicological, availability and solubility characteristics of extractables. Safety Risk categories were established based on certain scaled values for these characteristics, Total Risk Scores were calculated for each extractable and the extractables were categorized with respect to their safety risk based on these calculations.

Results The Total Risk Scores were normally distributed around a value of 20 to 23, corresponding to safety risk categories of moderate and intermediate risk. The range in Risk Scores defined by the mean ± one standard deviation encompassed the entire region of moderate and intermediate risk. Approximately 15% of the extractables were categorized as lowest risk while 3% of the extractables were categorized as highest risk.

Conclusions Categorization of extractables could facilitate the selection of materials for use in pharmaceutical systems, the analytical testing of extracts and the selection of target extractables.

KEY WORDS devices · extractables · leachables · parenteral packaging · safety assessment

INTRODUCTION

During their production, storage and use, pharmaceutical drug products encounter polymeric materials present in the product's manufacturing, packaging and delivery systems. During these encounters, the drug product and the materials may interact, resulting in the transfer of extractable materials from the polymer to the drug product. Such substances present in the drug product are called leachables. As users of the drug products are exposed to the leachables during their use of the drug product, leachables could represent a potential patient safety hazard. The magnitude of the patient safety risk posed by a given leachable can be estimated by two factors, the hazard presented by the leachables (reflecting their toxic potential) and the likelihood that users would be exposed to sufficient quantities of the leachables to pose a hazard. This approach is equivalent to the concept that risk is a combination of the probability of the occurrence of harm and the severity of the harm, as noted in ICH Q9 [1].

There are certain characteristics of polymeric materials and leachables that are readily recognized as potential hazard factors:

- the potential toxicity/mutagenicity of the leachable,
- the amount of the compound extract,
- the frequency that the compound is encountered in diverse materials, and
- the solubility of the leachable in the formulation.

If one could establish a semi-quantitative scale versus the largely qualitative generalizations noted above, and if the scale could be applied to the individual members of a population of extractables, then the individual members could be classified or rank-ordered in terms of their hazard potential.

In this manuscript, the safety risk represented by extractables is defined by two dimensions; the hazard (as established by the inherent toxicity of the extractable) and the probability of occurrence (as established by the frequency with which extractables are present in polymeric materials, the amounts at which the extractables are present in the materials and the propensity of the extractables to accumulate in the drug products as leachables). This partitioning is the basis of a Risk Evaluation Matrix, which was applied to over 500

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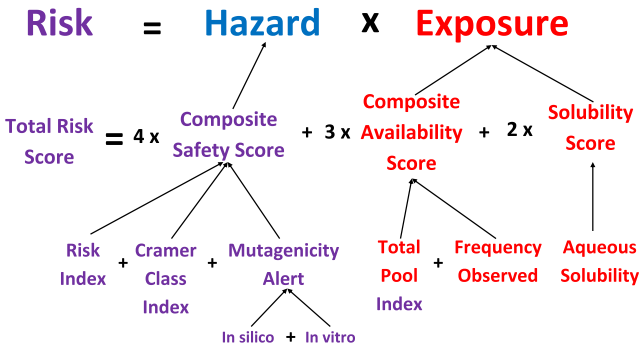

Fig. 1 Process flow diagram illustrating the calculation of the total risk score from its various components.

extractables for the purpose of stratifying the extractables in terms of their relative safety risk.

MATERIALS AND METHODS: THE RISK EVALUATION MATRIX

General Considerations

The safety qualification of polymeric materials, components and systems is driven largely by the principles of risk management, as opposed to the principles of risk avoidance. This is the case as it is largely impractical, if not impossible, to completely avoid the safety risks associated with leachables, as so doing would require that either (a) all leachables be avoided or (b) all leachables be toxicologically inert (that is, the leachable's physical, chemical and biological properties would be such that the leachable would have no adverse effect on user health and well-being).

The objective of stratifying a large population of extractables based on a semi-quantitative estimation of their associated safety risk is accomplished by establishing a Risk Evaluation Matrix and then applying that Matrix to the individual extractables to produce a Total Risk Score for each extractable (see Fig. 1). Broad safety risk categories were developed by applying certain constraints to the safety risk scoring process, thereby dividing the range of potential Total Risk Scores into safety categories. Based on their individual Total Risk Scores and the safety groupings, the individual extractables are classified.

In this exercise, the Risk Evaluation Matrix consisted of two primary inputs, including measures of the extractable's inherent toxic potential and the extractable's availability. The extractable's availability is further partitioned into two secondary inputs, the frequency with which the extractable is reported in the study of polymers used in pharmaceutical applications and the extractable's tendency to migrate out of those materials and into the drug product. These primary and secondary inputs were used to calculate the Total Risk Score for each individual extractable.

The Risk Evaluation Matrix is predicated on the generalization that the safety risk is greater when:

1. The extractable's toxic potential is higher,
2. The extractable's amount in the source material is higher,
3. The extractable is more frequently detected in diverse materials, and
4. The extractable is more soluble in aqueous drug products.

Safety Hazard

Considering the development and justification of the Risk Evaluation Matrix in greater detail, Table I considers the safety hazard posed by the extractable (when present as a

Table I Definition of the Safety Component of the Risk Evaluation Matrix

Risk index[a]		Cramer classification[b]		Mutagenicity alerts[c]		Safety risk
Criterion	Score	Criterion	Score	Criterion	Score	
RI > 10 mg/day	0	Class I	0	No alerts	0	Lower
<1 mg/day RI < 10 mg/day	1	Class 2	1	In vitro alert	1	
0.1 mg/day < RI < 1 mg/day	2	Class 3	2	In silico alert	2	
RI < 0.1 mg/day	3	–	–	Both in vitro and in silico	3	Higher

Composite safety score = risk index score + cramer score + mutagencity score

Composite safety score ranking

Composite Score	Categorization	Safety risk
0–1	Negligible safety risk	Lower
2–3	Lower safety risk	
4–5	Moderate safety risk	
6–8	Higher safety risk	Higher

[a] The Risk Index is an estimate of the toxic potential of a specific extractables, calculated per ref. [2]

[b] Established for either the extractable itself or its associated surrogate, per ref. [2]

[c] Reflects published in vitro mutagencity alerts as well as calculated in silico alerts per ref. [2]

leachable). The safety hazard is estimated by calculating a composite safety score for each extractable based on three criteria, the extractable's Risk Index, structure-activity analysis of the extractable (Cramer classification) and reported in vitro or in silico mutagencity Alerts. The source of the data used in the safety scoring is a compilation of safety data for extractables that has recently been published [2]. This compilation introduced the concept of the Risk Index, which is obtained by systematically applying uncertainty factors to available toxicological data (such as NOELs, LD50s) in a manner similar to, but not as rigorous as, the calculation of permissible daily exposure (PDE) values according to ICH.

An extractable's safety score is calculated as follows:

1. The range of risk index values is divided into four groups based on the magnitude of the RI. An extractable with a larger RI (higher amounts required to produce toxicity, therefore lesser safety hazard) is given a lower safety score and an extractable with a smaller RI (lesser amounts required to produce toxicity, therefore higher safety hazard) are given a higher safety score. Each RI group is given a point value (see Table I), based in part on a consideration of the previously reported distribution of the RI values. For example, the criterion for the highest risk index score of 3 was that the RI be less than 0.1 mg/day, which corresponded to the 95% percentile on the extractable's RI cumulative distribution plot.
2. The extractable is assigned a risk score based on its Cramer classification. Based on Quantitative Structure-Activity Relationships (QSAR), the Cramer classification is a rules-based process that sorts compounds into three classes; Class 1 (low risk of toxicity), Class 3 (either no basis to presume safety or positive indication of toxicity), and Class 2 (intermediate between 1 and 2). Somewhat arbitrarily, the Cramer classifications were given scores whose value increased with the increasing Cramer class.
3. Lastly, the extractable is assigned a risk score based on its mutagenitic potential, as evidenced by published in vitro or calculated in silico mutagenicity alerts. The magnitude of risk score related to mutagenicity alerts is established by the nature of the alert (in vitro or in silico) and whether there are re-enforcing alerts (both in vitro and in silico alerts). The in silico analysis was performed with the Benigni/Bossa rule base via ToxTree [3].
4. The composite safety score for each extractable is determined as the simple sum of the RI, Cramer and Alerts risk scores. On the basis of this process, safety risk scores can range from 0 (lower safety risk) to 8 (higher safety risk). This range was divided into smaller groups so as to provide each extractable with a "safety label".

Availability Score

In a similar manner, an extractable's availability score is calculated as follows (Table II), based on the accumulated experience gained by testing the many plastics represented in the RI database published in reference 2.

1. In many controlled extraction studies, the total pool of an extractable in the test material is either directly established or inferred. Four total pool categories for extractables

Table II Definition of the Availability Component of the Risk Evaluation Matrix

Anticipated Pool of the extractable[a]		Frequency with which the extractable is observed[b]		Safety risk
Criterion	Score	Criterion	Score	
Pool < 10 μg/g	0 (minor impurity, Impm)	Rare (uncommon within and across material types)	0	Lower
<10 μg/g < Pool < 10 μg/g	1 (major impurity, ImpM)	Frequent (common within a material class, uncommon across classes)	1	
<0.01% Pool < 0.1%	2 (minor ingredient, Ingm)	Common (Common both within a material class and across material classes)	2	
Pool > 0.1%	3 (major ingredient, IngM)			Higher
Composite availability score = pool score + frequency score				
Composite availability score ranking				
Composite score		Categorization		Safety Risk
0–1		Lower availability		Lower
2		Intermediate availability		
3		Moderate availability		
4–5		Higher availability		Higher

[a] This is the total amount of the extractable that is present in the test article

[b] This is a subjective estimate of how frequently this extractable is encountered in the materials that have been tested by the Baxter organization

were established, as it is the case that the higher the pool, the larger the amount of extractable that could leach into the drug product and the greater the risk of an adverse safety impact. These total pool classes range from extractables that are present with relatively low pools (that is, as impurities in the polymer) to extractables that were present with relatively high pools (that is, as ingredients in the polymer). The criterion for the lowest risk class (lowest pool) was chosen at 10 μg/g, as this value has been established to be a reasonable target level for characterizing materials for extractables [4, 5]. The criterion for the highest risk class (highest pool), 1,000 μg/g (or 0.1% by weight), is consistent with lower levels at which additives are intentionally added to plastic materials

2. The second dimension of the availability score dealt with the frequency with which extractables were detected in the materials upon which the RI Index database was established, the concept being that the more frequently the extractables were detected in materials, the more often the extractables would be encountered in pharmaceutical systems and thus the greater the safety risk. Three levels were created for establishing the frequency score with a lower score being assigned to those extractables which were rare (i.e., uncommonly encountered even within a material class) and a higher score being assigned to extractables that were commonly encountered across multiple material classes.
3. The composite availability score for each extractable is determined as the simple sum of the frequency and anticipated pool scores. On the basis of this process, composite availability scores can range from 0 (lower availability) to 5 (higher availability). This range was divided into smaller groups so as to provide each extractable with an "availability label".

Solubility Score

Lastly, an extractable's solubility score was calculated as follows (Table III), based on published aqueous solubility data over the pH range of pH 2 to pH 10 [6]. Four solubility classes were established, based on the observation that the higher the solubility of an extractable, the larger the amount of extractable that could leach into the drug product and the greater the risk of an adverse safety impact and roughly corresponding to extractables with low aqueous solubilities (making them essentially insoluble in the drug product) to extractables with relatively higher solubilities (making them highly soluble in and available to the drug product). The criterion for an insoluble extractable was set at 0.1 mg/L to be consistent with a safety threshold relevant for a parenteral drug product. For example, an acceptable daily intake of 120 μg/day has been proposed for genotoxic and carcinogenic impurities in drug products whose duration of exposure is less than 14 days (corresponding to an acute versus a chronic therapy) [7]. If this daily intake were associated with a daily dose volume of 1 L (not untypical of parenteral products such as LVPs), then the corresponding threshold concentration of a leachable in the drug product would be 0.12 mg/L, which is essentially the same as the insoluble criterion. The criteria for the other solubility classes were set at factor of ten steps up from the insolubility criterion.

Table III Definition of the Solubility Component of the Risk Evaluation Matrix

Criterion[a]	Solubility score	Safety risk
Solubility < 0.1 mg/L	1 (insoluble)	Lower
0.1 mg/L < Solubility < 1 mg/L	2 (relatively insoluble)	
1 mg/L < Solubility < 10 mg/L	3 (relatively soluble)	
Solubility > 10 mg/L	4 (soluble)	Higher

[a] The solubility was established over a pH range of 2 to 10. The solubility that was used to classify an extractable was the highest solubility reported for that extractable over this pH range

Table IV Calculation of the total risk score (TRS)

Total risk score = 4 × (Composite safety score) + 3 × (Composite availability score) + 2 × (Solubility score)

Total risk score ranking

Total risk score	Categorization	Safety risk
0–13[a]	Lowest Risk	Lower
14–22[b]	Moderate Risk	
23–35[c]	Intermediate Risk	
36 or greater[d]	Highest Risk	Higher

[a] This is derived by minimizing the safety risk in each of the individual risk components as follows: safety risk (low risk, score 2 or less), availability risk (low availability, score of 1), and solubility (insoluble, score of 1). High end of risk score range = 4(2) + 3(1) +2(1) = 13.

[b] This is derived by establishing the safety risk in each of the individual risk components as follows: safety risk (low risk, highest score of 3), availability risk (intermediate availability, score of 2), and solubility (relatively insoluble, score of 2). High end of risk score range = 4(3) + 3(2) +2(2) = 22

[c] This is derived by establishing the safety risk in each of the individual risk components as follows: safety risk (moderate risk, score 5 or less), availability risk (moderate availability, score of 3), and solubility (relatively soluble, score of 3). High end of risk score range = 4(5) + 3(3) +2(3) = 35

[d] The maximum total risk score is obtained using a safety risk (high risk, score of 8), availability risk (high availability, score of 5), and solubility (soluble, score of 4), producing a maximum risk score = 4(8) + 3(5) +2(4) = 55

Table V Compilation of risk data, group 1 extractables

Extractable's ID		Safety component		Availability component				Solubility component				Total Risk score
Name	CAS RN	Score	Rank	Level	Occurrence	Score	Rank	Solubility, mg/L		Score	Rank	
								pH 2	pH 10			
2,4-Dichlorobenzoic acid	50–84–0	3	Low	Impm	Rare	0	Low	320	380,000	4	Soluble	20
Glycerine	56–81–5	0	Negligible	ImpM	Freq	2	Int	715,000		4	Soluble	14
Palmitic Acid	57–10–3	1	Negligible	ImpM	Com	3	Mod	5	28,000	4	Soluble	21
Stearic acid	57–11–4	1	Negligible	IngM	Com	5	High	1	65,000	4	Soluble	27
Urea	57–13–6	1	Negligible	Impm	Rare	0	Low	825,000		4	Soluble	12
Propylene glycol	57–55–6	0	Negligible	ImpM	Freq	2	Int	380,000		4	Soluble	14
Linoleic acid	60–33–3	2	Low	Impm	Freq	1	Low	4	23,000	4	Soluble	19
Formic acid	64–18–6	0	Negligible	IngM	Com	5	High	910,000		4	Soluble	23
Acetic acid	64–19–7	0	Negligible	IngM	Com	5	High	900,000		4	Soluble	23
Benzoic acid	65–85–0	1	Negligible	ImpM	Freq	3	Mod	5,700	1,000,000	4	Soluble	21
Hexanal	66–25–1	3	Low	Impm	Rare	0	Low	3,100		4	Soluble	20
Isopropanol	67–63–0	0	Negligible	ImpM	Freq	3	Mod	141,000		4	Soluble	17
Acetone	67–64–1	0	Negligible	Impm	Rare	0	Low	94,700		4	Soluble	8
Dimethylformamide	68–12–2	2	Low	ImpM	Rare	1	Low	1,000,000		4	Soluble	19
p-Toluenesulfonamide	70–55–3	4	Moderate	ImpM	Common	3	Mod	3,100		4	Soluble	33
1-Butanol	71–36–3	0	Negligible	Impm	Freq	1	Low	48,000		4	Soluble	11
1-Pentanol	71–41–0	2	Low	Impm	Rare	0	Low	21,000		4	Soluble	16
4-Chlorobenzoic acid	74–11–3	5	Moderate	Impm	Rare	0	Low	930	1,000,000	4	Soluble	28
Ethyl aldehyde	75–07–0	3	Low	Impm	Rare	0	Low	53,700		4	Soluble	20
Carbon disulfide	75–15–0	6	High	Impm	Rare	0	Low	380		4	Soluble	32
2,2-Dimethylpropanoic acid	75–98–9	2	Low	Impm	Rare	0	Low	27,000	1,000,000	4	Soluble	16
Tributyl acetylcitrate	77–90–7	2	Low	IngM	Freq	4	High	20		4	Soluble	28
Diethoxydimethylsilane	78–62–6	2	Low	Ingm	Freg	3	Mod	47,000		4	Soluble	25
2-Butanone	78–93–3	1	Negligible	Impm	Rare	0	Low	47,000		4	Soluble	12
Propionic acid	79–09–4	0	Negligible	Impm	Freq	1	Low	45,600	1,000,000	4	Soluble	11
Hydroxyacetic acid	79–14–1	1	Negligible	Impm	Freq	1	Low	1,000,000		4	Soluble	15
2-Hydroxypropanoic acid	79–33–4	1	Negligible	Impm	Rare	0	Low	809,000	1,000,000	4	Soluble	12
1,1,2,2-Tetrachloroethane	79–34–5	4	Moderate	Impm	rare	0	low	570		4	Soluble	24
Bisphenol A	80–05–7	4	Moderate	ImpM	Freq	2	Int	71	110	4	Soluble	30
4-tert-Amylphenol	80–46–6	0	Negligible	Impm	Rare	0	Low	380	590	4	Soluble	8
Methacrylic acid, methyl ester	80–62–6	2	Low	ImpM	Freq	2	Int	25,000		4	Soluble	22
Diethyl phthalate	84–66–2	3	Low	ImpM	Freq	2	Int	530		4	Soluble	26
Diisobutyl phthalate	84–69–5	2	Low	ImpM	Freq	2	Int	31		4	Soluble	22
Dibutyl phthalate	84–74–2	2	Low	ImpM	Freq	2	Int	25		4	Soluble	22
Phthalic anhydride	85–44–9	5	Moderate	Impm	Freq	2	Int	15		4	Soluble	34
Benzyl butyl phthalate	85–68–7	2	Low	Impm	Freq	1	Low	7.5		3	Rsol	17
2-Furancarboxylic acid	88–14–2	4	Moderate	Impm	Rare	0	Low	9,000	1,000,000	4	Soluble	24
o-Toluenesulfonamide	88–19–7	2	Low	ImpM	Common	3	Int	27,000	45,000	4	Soluble	25
3,5-Di-tert-butyl-4-hydroxybenzyl alcohol	88–26–6	2	Low	Imp M	Common	3	Int	330		4	Soluble	25
Phthalic acid	88–99–3	4	Moderate	ImpM	Freq	2	Int	7,500	100,000	4	Soluble	30
o-Hydroxybiphenyl	90–43–7	6	High	Impm	Rare	0	Low	170	340	4	Soluble	32
α-Phenylbenzenemethanol	91–01–0	3	Low	Impm	Freq	1	Low	2,000		4	Soluble	23
Hexanoic acid, 2-ethyl-, diester with triethylene glycol	94–28–0	3	Low	Impm	Rare	0	Low	19		4	Soluble	20
2-Ethyl-1,3-hexanediol	94–96–2	3	Low	Impm	Rare	0	Low	6,100		4	Soluble	20
Benzothiazole	95–16–9	3	Low	Impm	Freq	1	Low	37,000		4	Soluble	23
o-Xylene	95–47–6	2	Low	Impm	Rare	0	Low	1.1		3	RSol	14

Table V (continued)

Extractable's ID		Safety component		Availability component				Solubility component				Total Risk score
Name	CAS RN	Score	Rank	Level	Occurrence	Score	Rank	Solubility, mg/L		Score	Rank	
								pH 2	pH 10			
1,2,4-Trimethylbenzene	95–63–6	0	Negligible	Impm	Rare	0	Low	3.2		4	Soluble	8
2,4-Di-t-butyl phenol	96–76–4	3	Low	ImpM	Common	3	Mod	120		4	Soluble	29
1-Methylethylbenzene	98–82–8	3	Low	Impm	Rare	0	Low	43		4	Soluble	20
Acetophenone	98–86–2	3	Low	ImpM	Common	3	Mod	2,400		4	Soluble	29
2-Propyl valeric acid	99–66–1	3	Low	Impm	Rare	0	Low	2,300	999,000	4	Soluble	20
Terephthalic acid	100–21–0	0	Negligible	ImpM	Freq	2	Int	3,000	1,000,000	4	Soluble	14
Ethyl benzene	100–41–4	2	Low	Impm	Freq	1	Low	110		4	Soluble	19
Styrene	100–42–5	1	Negligible	ImpM	Freq	2	Int	300		4	Soluble	18
4-Cyanocyclohexene	100–45–8	4	Moderate	Impm	Freq	1	low	1,200		4	Soluble	27
Benzyl alcohol	100–51–6	2	Low	ImpM	Freq	2	Int	4,700		4	Soluble	22
Benzaldehyde	100–52–7	6	High	ImpM	Freq	2	Int	2,100		4	Soluble	38
Diphenylmethane diisocyanate	101–68–8	5	Moderate	Impm	Freq	1	Low	8		3	RSol	29
Diphenyl ether	101–84–8	2	Low	Impm	Freq	1	Low	44		4	Soluble	19
2-Ethylhexyl acrylate	103–11–7	3	Low	ImpM	Freq	2	Int	20		4	Soluble	26
Bis(2-ethylhexyl)adipate	103–23–1	2	Low	Ingm	Freq	3	Mod	0.67		2	Rinsol	21
Dibenzyl amine	103–49–1	4	Moderate	IngM	Freq	5	High	734,000	610	4	Soluble	39
Dihydro-5-pentyl-2(3H)-furanone	104–61–0	2	Low	Impm	Freq	1	Low	1,560		4	Soluble	19
2-Ethyl-1-hexanol	104–76–7	3	Low	ImpM	Common	3	Med	1,700		4	Soluble	29
p-Methylbenzaldehyde	104–87–0	3	Low	Impm	Freq	1	Low	1,100		4	Soluble	23
1,4-Cyclohexanedimethanol	105–08–8	2	Low	Impm	Freq	1	Low	32,000		4	Soluble	19
1,1-Diethoxyethane	105–57–7	2	Low	Impm	Rare	0	Low	53,000		4	Soluble	16
Caprolactam	105–60–2	2	Low	IngM	Common	5	High	26,000		4	Soluble	31
3-Heptanone	106–35–4	2	Low	Impm	Freq	1	Low	5,000		4	Soluble	19
p-Xylene	106–42–3	1	Negligible	Imgm	Freq	1	Low	100		4	Soluble	15
Acrylonitrile	107–13–1	6	High	ImgM	Freq	2	Int	99,200		4	Soluble	38
Ethylene glycol	107–21–1	2	Low	Ingm	Freq	3	Mod	538,000		4	Soluble	25
3-Methyl-2-butenal	107–86–8	4	Moderate	Impm	Rare	0	Low	26,000		4	Soluble	24
Butyric acid	107–92–6	1	Negligible	ImpM	Freq	2	Int	45,000	1,000,000	4	Soluble	18
Methyisobutylketone	108–10–1	2	Low	Impm	Rare	0	Low	12,000		4	Soluble	16
3,5-Dimethylphenol	108–68–9	1	Negligible	Impm	Freq	1	Low	5,900		4	Soluble	15
Toluene	108–88–3	3	Low	ImpM	Freq	2	Int	320		4	Soluble	26
Cyclohexanol	108–93–0	1	Negligible	Impm	Freq	1	Low	44,000		4	soluble	15
Cyclohexanone	108–94–1	2	Low	Ingm	Freq	3	Mod	15,000		4	Soluble	25
Phenol	108–95–2	3	Low	ImpM	Freq	2	Int	97,000		4	Soluble	26
3-Hydroxypyridine	109–00–2	5	Moderate	Impm	Freq	1	Low	1,000,000	887,000	4	Soluble	31
Butanoic acid, butyl ester	109–21–7	0	Negligible	Impm	Rare	0	low	1,900		4	Soluble	8
Pentanoic acid	109–52–4	1	Negligible	Impm	Freq	1	Low	21,000	1,000,000	4	Soluble	15
Tetrahydrofuran	109–99–9	2	Low	ImpM	Freq	2	Int	31,000		4	Soluble	22
Succinic acid	110–15–6	4	Moderate	Impm	Freq	1	Low	325,000	1,000,000	4	Soluble	27
Pentanal	110–62–3	6	High	Impm	Freq	1	Low	6,600		4	Soluble	35
Tetramethylene glycol	110–63–4	2	Low	ImpM	Freq	2	Int	180,000		4	Soluble	22
2-Ethoxyethanol	110–80–5	0	Negligible	ImpM	Freq	2	Int	407,000		4	Soluble	14
Pyridine	110–86–1	5	Moderate	ImpM	Freq	2	Int	100,000	893,000	4	Soluble	34
Piperidine	110–89–4	3	Low	ImpM	Freq	2	Int	1,000,000	367,000	4	Soluble	26
Pentanedioic acid	110–94–1	1	Negligible	Impm	Rare	0	Low	164,000	1,000,000	4	Soluble	12
Squalene	111–02–4	0	Negligible	Impm	Rare	0	Low	0.0001		0	Insol	0
2-Octanone	111–13–7	3	Low	Impm	Rare	0	Low	2,300		4	Soluble	20

Table V (continued)

Extractable's ID		Safety component		Availability component				Solubility component				Total Risk score
Name	CAS RN	Score	Rank	Level	Occurrence	Score	Rank	Solubility, mg/L		Score	Rank	
								pH 2	pH 10			
Heptanoic acid	111–14–8	0	Negligible	Impm	Freq	1	Low	4,400	1,000,000	4	Soluble	11
Sebacic acid	111–20–6	1	Negligible	ImpM	Freq	2	Int	3,800	1,000,000	4	Soluble	18
1-Hexanol	111–27–3	2	Low	ImpM	Freq	2	Int	8,800		4	Soluble	22
Diethylene glycol	111–46–6	0	Negligible	Ingm	Freq	3	Mod	1,000,000		4	Soluble	17
Octdecanoic acid, 2-hydroethyl ester	111–60–4	2	Low	Impm	Rare	0	Low	2.5		3	Rsol	14
Octadecanoic acid, ethyl ester	111–61–5	1	Negligible	ImpM	Freq	2	Int	0.29		2	RInsol	14
Octadecenoic acid, ethyl ester	111–62–6	1	Negligible	Impm	Rare	0	Int	0.53		2	RInsol	8
1-Heptanol	111–70–6	2	Low	Impm	Freq	1	Low	3,400		4	Soluble	19
2-(1-Butoxy) ethanol	111–76–2	0	Negligible	Impm	Freq	1	Low	89,000		4	Soluble	11
Octanol	111–87–5	1	Negligible	Impm	Freq	1	Low	1,200		4	Soluble	15
2-(2-ethoxyethoxy)ethanol	111–90–0	1	Negligible	ImpM	Freq	2	Int	590,000		4	Soluble	18
Dibutyl amine	111–92–2	5	Moderate	ImpM	Freq	2	Int	1,000,000	74,000	4	Soluble	34
Nonanoic acid	112–05–0	1	Negligible	ImpM	Freq	2	Int	97	1,000,000	4	Soluble	18
2-(2-Ethoxyethoxy) ethyl acetate	112–15–2	1	Negligible	Impm	Rare	0	Low	72,000		4	Soluble	12
Triethylene glycol	112–27–6	0	Negligible	ImpM	Com	3	Mod	1,000,000		4	Soluble	17
2-(2-Butoxyethoxy)ethanol	112–34–5	2	Low	Impm	Freq	1	Low	120,000		4	Soluble	19
Undecanoic acid	112–37–8	2	Low	Impm	Freq	1	Low	200	1,000,000	4	Soluble	19
Hexadecanoic acid, methyl ester	112–39–0	1	Negligible	Impm	Freq	1	Low	2.3		3	RSol	13
1-Dodecene	112–41–4	1	Negligible	Impm	Rare	0	Low	0.007		0	Insol	4
Dodecanol	112–53–8	1	Negligible	IimpM	Freq	2	Int	9.3		4	Soluble	18
Dodecanal	112–54–9	2	Low	Impm	Rare	0	Low	33		4	Soluble	16
Tetraethylene glycol	112–60–7	2	Low	ImpM	Freq	2	Int	1,000,000		4	Soluble	22
Octadecenoic acid, methyl ester	112–62–9	1	Negligible	Impm	Rare	0	Low	1.1		3	Rsol	10
Tetradecanol	112–72–1	1	Negligible	ImpM	Freq	2	Int	0.58		2	Rinsol	14
Oleic acid	112–80–1	3	Low	Ingm	Freq	3	Mod	0.008	34	3	RSol	27
Erucamide	112–84–5	1	Low	IngM	Common	5	High	0.1		2	RInsol	23
Oleonitrile	112–91–4	3	Low	ImpM	Freq	2	Int	0.4		2	RInsol	22
Octadecanol	112–92–5	0	Negligible	Impm	Common	2	Inter	0.001		1	Insol	8
Triphenylphosphate	115–86–6	3	Low	ImpM	Freq	2	Int	7.2		3	RSol	24
Bis-(2-ethylhexyl) phthalate	117–81–7	3	Low	IngM	Frequent	4	High	0.11		2	RInsol	28
Octyldecyl phthalate	119–07–3	3	Low	Impm	Rare	0	Low	0.025		1	Insol	14
Benzophenone	119–61–9	3	Low	ImpM	Freq	2	Int	150		4	Soluble	26
9,10-Dihydroxystearic acid	120–87–6	2	Low	IngM	Common	5	High	60	316,000	4	Soluble	31
4-Hydroxy-3-methoxybenzoic acid	121–34–6	1	Negligible	Impm	Rare	0	Low	9,100	1,000,000	4	Soluble	12
1,3-Benzenedicarboxylic acid	121–91–5	0	Negligible	Ingm	Freq	3	Mod	9,800	1,000,000	4	Soluble	17
Triisopropanolamine	122–20–3	0	Negligible	ImpM	Freq	2	Int	1,000,000	100,000	4	Soluble	14
2-Ethyl-1-hexanal	123–05–7	3	Low	ImpM	Freq	2	Int	770		4	Soluble	26
Nonanoic acid, ethyl ester	123–29–5	1	Negligible	Inpm	Rare	0	Low	190		4	Soluble	12
Azelaic acid	123–99–9	1	Negligible	Impm	Freq	1	Low	8,800	999,000	4	Soluble	15
Adipic acid	124–04–9	2	Low	IngM	Freq	3	Mod	76,000	1,000,000	4	Soluble	25
Octanoic acid	124–07–2	0	Negligible	ImpM	Freq	2	Int	2,200	999,000	4	Soluble	14
Tetradecanoic acid, methyl ester	124–10–7	1	Negligible	Impm	Freq	1	Low	9.7		4	Soluble	15
Octanal	124–13–0	4	Moderate	Impm	Freq	1	Low	690		4	Soluble	27
Nonanal	124–19–6	2	Low	Impm	Freq	1	Low	330		4	Soluble	19
Octadecanamide	124–26–5	0	Negligible	Impm	Freq	1	Low	0.82		2	Risol	7
Stearylamine	124–30–1	2	Low	Impm	Freq	1	Low	21,000	8.4	4	Soluble	19
Neopentyl glycol	126–30–7	0	Negligible	ImpM	Freq	2	Int	120,000		4	Soluble	14

Table V (continued)

Extractable's ID		Safety component		Availability component				Solubility component				Total Risk score
Name	CAS RN	Score	Rank	Level	Occurrence	Score	Rank	Solubility, mg/L		Score	Rank	
								pH 2	pH 10			
Tributyl phosphate	126–73–8	5	Moderate	Impm	Freq	1	Low	640		4	Soluble	31
2,4,7,9-Tetramethyl-5-decyn-4,7-diol	126–86–3	4	Moderate	Impm	Rare	0	Low	10		4	Soluble	24
Diphenyl sulfone	127–63–9	3	Low	Impm	Freq	1	Low	130		4	Soluble	23
2,6-Di-t-butyl-4-methyl phenol	128–37–0	3	Low	IngM	Common	5	High	66		4	Soluble	35
2,6-Di-tert-butylphenol	128–39–2	4	Moderate	ImpM	Common	3	Mod	140		4	Soluble	33
1,2-Benzenecarboxylic acid, monobutyl ester	131–70–4	5	Moderate	Impm	Freq	1	Low	490	640,000	4	Soluble	31
Tetramethylbutyl phenol	140–66–9	3	Low	Impm	Freq	1	Low	62	110	4	Soluble	23
2-Ethylhexyl fumarate	141–02–6	4	Moderate	Impm	Freq	1	Low	1.7		3	Rsol	25
Ricinoleic acid	141–22–0	0	Negligible	Impm	Freq	1	Low	30	1,000,000	4	Soluble	11
Decamethyltetrasiloxane	141–62–8	4	Moderate	ImpM	Freq	2	Int	65		4	Soluble	30
1,1,1,5,5,5-Hexamethyl-3, 3-bisoxytrisiloxane	141–63–9	3	Low	ImpM	Freq	2	Int	7.7		3	Rsol	24
Ethyl acetate	141–78–6	1	Negligible	ImpM	Common	3	Mod	39,000		4	Soluble	21
Hexanoic acid	142–62–1	0	Negligible	ImpM	Common	3	Mod	9,800	1,000,000	4	Soluble	17
Dodecanoic acid	143–07–7	1	Negligible	ImpM	Common	3	Mod	98	531,000	4	Soluble	21
Nonanol	143–08–8	2	Low	ImpM	Freq	2	Low	390		4	Soluble	22
2-Mercaptobenzothiazole	149–30–4	5	Moderate	ImpM	Freq	2	Int	99	250	4	Soluble	34
Caproic acid	149–57–5	1	Negligible	ImpM	Common	3	Mod	2,300	999,000	4	Soluble	21
4-Methoxyphenol	150–76–5	1	Negligible	Impm	Freq	1	Low	10,000		4	Soluble	15
Cyclohexene oxide	286–20–4	6	High	Impm	Freq	1	Low	32,000		4	Soluble	35
Oleamide	301–02–0	3	Low	ImpM	Common	3	Mod	1.5		3	Rsol	27
Decanoic acid	334–48–5	1	Negligible	ImpM	Common	3	Mod	450	1,000,000	4	Soluble	21
3,5-Dimethylbenzoic acid	499–06–9	2	Low	Impm	Freq	1	Low	92	100,000	4	Soluble	19
Caprolactone	502–44–3	2	Low	Impm	Freq	1	Low	26,000		4	Soluble	19
3-Methylbutanoic acid	503–74–2	1	Negligible	Impm	Freq	1	Low	23,000	1,000,000	4	Soluble	15
Heptadecanoic acid	506–12–7	2	Low	Impm	Common	2	Int	2.5	14,000	3	Rsol	20
Abietic acid	514–10–3	2	Low	ImpM	Freq	2	Int	0.008	42	2	RInsol	18
2-Chloroacetophenone	532–27–4	5	Moderate	Impm	Freq	1	Low	1,500		4	Soluble	31
Decamethylcyclopentasiloxane	541–02–6	2	Low	ImpM	Freq	2	Int	91,000	84,000	4	Soluble	22
Myristic acid	544–63–8	1	Negligible	Ingm	Common	4	High	22	120,000	4	Soluble	24
Octamethylcyclotetrasiloxane	556–67–2	4	Moderate	ImpM	Freq	2	Int	<0.1		1	Insol	24
5-Quinolinol	578–67–6	5	Moderate	Impm	rare	0	Low	91,000	84,000	4	Soluble	28
2-Methyl cyclohexanol	583–59–5	3	Low	Impm	Freq	1	Low	21,000		4	Soluble	23
3-Heptanol	589–82–2	3	Low	Impm	Common	2	Low	4,600		4	Soluble	26
Propanoic acid, butyl ester	590–01–2	1	Negligible	Impm	rare	0	Low	3,900		4	Soluble	12
2-Pyrrolidinone	616–45–5	3	Low	Impm	Freq	1	Low	67,000		4	Soluble	23
α-α-Dimethylbenzenemethanol	617–94–7	4	Moderate	Impm	Freq	1	Low	12,000		4	Soluble	27
m-Methylbenzaldehyde	620–23–5	2	Low	Impm	Freq	1	Low	7.2		3	RSol	17
Hexanedioic acid, dimethyl ester	627–93–0	2	Low	Impm	Freq	1	Low	14,000		4	Soluble	19
1,6-Hexanediol	629–11–8	0	Negligible	Impm	Freq	1	Low	39,000		4	Soluble	11
Isophthalic acid, diethyl ester	636–09–9	2	Low	Impm	Freq	1	Low	310		4	Soluble	19
Diethyl isophthalate	636–53–3	2	Low	ImpM	Freq	2	Int	290		4	Soluble	22
2,6-Di-tert-butyl-p-benzoquinone	719–22–2	3	Low	Impm	Freq	1	Low	51		4	Soluble	23
1-Cyclohexyl-2-ethanone	823–76–7	1	Negligible	Impm	Rare	0	Low	4,000		4	Soluble	12
1-Methyl-2-pyrrolidinone	872–50–4	3	Low	Impm	Freq	1	Low	82,000		4	Soluble	23
2-Cyclohexene-1-one	930–68–7	5	Moderate	Impm	Freq	1	Low	16,000		4	Soluble	31
Diphenylsilanediol	947–42–2	3	Low	ImpM	Freq	2	Int	110		4	Soluble	26

Table V (continued)

Extractable's ID		Safety component		Availability component				Solubility component				Total Risk score
Name	CAS RN	Score	Rank	Level	Occurrence	Score	Rank	Solubility, mg/L		Score	Rank	
								pH 2	pH 10			
Pentadecanoic acid	1002–84–2	2	Low	Impm	Freq	1	Low	11	58,000	4	Soluble	19
1,1′-Carbonothiobis-piperidine	1013–92–9	6	High	Impm	Freq	1	Low	110		4	Soluble	35
Trimethylsilanol	1066–40–6	2	Low	ImpM	Freq	2	Int	70,000		4	Soluble	22
1,1,3,3-Tetramethyl-1,3-disiloxanediol	1118–15–6	3	Low	Impm	Freq	1	Low	14,000		4	Soluble	23
Pentanedioic acid, dimethyl ester	1119–40–0	1	Negligible	Impm	Freq	1	Low	27,000		4	Soluble	15
3,5-Di-t-butyl-4-hydroxybenzaldehyde	1620–98–0	4	Moderate	ImpM	Common	3	Mod	26	1,200	4	Soluble	33
3,3′-Oxybispropanenitrile	1656–48–0	3	Low	Impm	Freq	1	Low	36,000		4	Soluble	23
Dehydroabietic acid	1740–19–8	2	Low	Ingm	Common	4	High	3.9	21,000	3	Rsol	26
Irganox 1076	2082–79–3	3	Low	IngM	Common	5	High	0.0004		0	Insol	27
Lauryl acrylate	2156–97–0	1	Negligible	Impm	Freq	1	Low	9.6		3	RSol	13
Vinyl caprolacam	2235–00–9	4	Moderate	Impm	Freq	1	Low	3,100		4	Soluble	27
Monoethyl phthalate	2306–33–4	6	High	ImpM	Freq	2	Int	3,300	180,000	4	Soluble	38
Drometrizole	2440–22–4	3	Low	Impm	Freq	1	Low	16	1,900	4	Soluble	23
9,10-Epoxy stearic acid	2443–39–2	6	High	Ingm	Freq	3	Mod	3	17,000	3	RSol	39
3-Methyl-1,3-bis(hydroxy)butane	2568–33–4	3	Low	Impm	Rare	0	Low	12	2,000	4	Soluble	20
1-Piperidinecarboxaldehyde	2591–86–8	3	Low	Impm	Freq	1	Low	22,000		4	Soluble	23
Hexaethylene glycol	2615–15–8	3	Low	Impm	Freq	1	Low	1,000,000		4	Soluble	23
Dihydrogenmonolauryl phosphate	2627–35–2	1	Negligible	Impm	Common	2	Int	690	999,000	4	Soluble	18
Tris(2-ethylhexyltrimellitate)	3319–31–1	2	Low	IngM	Freq	4	High	1		2	Risnsol	24
Nonaethylene glycol	3386–18–3	3	Low	ImpM	Freq	2	Int	990,000		4	Soluble	26
N-Butyl-benzenesulfonamide	3622–84–2	4	Moderate	ImpM	Freq	2	Int	940		4	Soluble	30
2-Pentyl furan	3777–96–3	4	Moderate	Impm	Freq	1	Low	290		4	Soluble	27
2-Butyl-1-octanol	3913–02–8	3	Low	Impm	Freq	1	Low	13		4	Soluble	23
Isophorone diisocyanate	4098–71–9	4	Moderate	Impm	Freq	1	Low	24		4	Soluble	27
Hexadecanoic acid, 2-hydroxyethyl ester	4219–49–2	1	Negligible	Impm	Freq	1	Low	10		4	Soluble	15
6-Chlorohexanoic acid	4224–62–8	5	Moderate	Impm	Freq	1	Low	7,100	1,000,000	4	Soluble	31
Mono-(2-ethylhexyl) phthalate	4376–20–9	2	Low	Ingm	Common	4	High	33	33,000	4	Soluble	28
1,4-Dioxacyclotridecane-5,13-dione	4471–27–6	1	Negligible	ImpM	Freq	2	Int	26,000		4	Soluble	18
Pentaethylene glycol	4792–15–8	1	Negligible	ImpM	Freq	2	Int	1,000,000		4	Soluble	18
Cyclohexaneacetic acid	5292–21–7	1	Negligible	Impm	Rare	0	Low	3,700	1,000,000	4	Soluble	12
1,1′-Carbonylbispiperdine	5395–04–0	4	Moderate	Impm	Freq	1	Low	450		4	Soluble	27
1,4-Dioxatetradecane-5,14-dione	5578–82–5	1	Negligible	ImpM	Freq	2	Int	1,500		4	Soluble	18
Irganox 1010	6683–19–8	2	Low	IngM	Common	5	High	0.00001		1	Insol	25
Terephthalic acid, diethylhexyl ester	6422–86–2	3	Low	ImpM	Freq	2	Int	0.07		1	Insol	20
3-(4-Hydroxyphenyl)-2-phenol	7400–08–0	3	Low	Impm	Freq	1	Low	4,800	1,000,000	4	Soluble	23
2-Hydroxy-2-methylpropiophenone	7473–98–5	4	Moderate	Impm	Freq	1	Low	4,400		4	Soluble	27
Metasilicic acid	7699–41–4	3	Low	Ingm	Freq	3	Mod	<0.1		1	Insol	23
Trition X-100	9002–93–1	1	Negligible	ImpM	Freq	2	Int	1,000,000		4	Soluble	18
Polyvinylpyrrolidone	9003–39–8	2	Low	ImpM	Freq	2	Low	> 10		4	Soluble	22
Cellulose diacetate	9035–69–2	1	Negligible	ImpM	Freq	2	Low	> 10		4	Soluble	18
Silicic acid	10193–36–9	4	Moderate	Ingm	Freq	3	Mod	164,000		4	Soluble	33
2-Cyanoacetic acid, 2-methoxyethyl ester	10258–54–5	3	Low	Impm	Rare	0	Low	273,000	1,000,000	4	Soluble	20
2,6-Di-(t-butyl)-4-hydroxy-4-methyl-2,5-cyclohexadien-1-one	10396–80–2	5	Moderate	Impm	Freq	1	Low	640		4	Soluble	31
1,6-Hexanediol diacrylate	13048–33–4	1	Negligible	Impm	Freq	1	Low	680		4	Soluble	15

Table V (continued)

Extractable's ID		Safety component		Availability component				Solubility component				Total Risk score
Name	CAS RN	Score	Rank	Level	Occurrence	Score	Rank	Solubility, mg/L		Score	Rank	
								pH 2	pH 10			
Trimethyolpropane triacrylate	15625–89–5	3	Low	Impm	Freq	1	Low	470		4	soluble	23
2-Heptenoic acid	18999–28–5	1	Negligible	Impm	Rare	0	Low	2,200	100,000	4	Soluble	12
3,5-Bis(1,1-dimethylethyl)-4-hydroxy-benzenepropanoic acid	20170–32–5	2	Low	Impm	Freq	1	Low	86	465,000	4	Soluble	19
5-(Decahydro-5,5,8-trimethyl-2-methylene-1-napthalenyl)-3-methyl-2-pentenoic acid	24470–48–2	4	Moderate	Impm	Rare	0	Low	1.5	76,000	3	Rsol	22
Cis-9,10-epoxyoctadecanoic acid	24560–98–3	5	Moderate	ImpM	Freq	2	Inter	3	17,000	3	Rsol	32
2,2-Dimethoxy-1,2-diphenyl ethanone	24650–42–8	5	Moderate	Impm	Rare	0	Low	150		4	Soluble	28
Polyethylene terephthalate	25038–59–9	3	Low	IngM	Freq	4	High	< 0.1		1	Insol	26
Benzene dicarboxylic acid, diisooctyl ester	27554–26–3	3	Low	Ingm	Freq	3	Mod	< 0.1		1	Insol	23
Glyceryl monostearate	31566–31–1	2	Low	ImpM	Freq	2	Low	> 10		4	Soluble	22
Irgafos 168	31570–04–4	3	Low	IngM	Common	5	High	0.001		1	Insol	29
15-Crown-5	33100–27–5	3	Low	ImpM	Freq	2	Low	767,000		4	Soluble	26
1-Hexadecanol	36653–82–4	2	Low	Impm	Freq	1	Low	0.03		1	Insol	13
Tri(propylene glycol) diacrylate	42978–66–5	4	Moderate	Impm	Freq	1	Low	4,000		4	Soluble	27
2,2,6,6-Tetramethypiperidinol	52722–86–8	3	Low	Impm	Freq	1	Low	1,000,000	330,000	4	Soluble	23
25-Crown-5	56890–57–4	5	Moderate	ImpM	Freq	2	Low	43,000		4	Soluble	34
Dipropylene glycol diacrylate	57472–68–1	3	Low	Impm	Freq	1	Low	5,200		4	Soluble	23
2-[1-4-Cyano-1,2,3,4-tetrahydronapthyl)]propanenitrile	57964–39–3	4	Moderate	Impm	Freq	1	Low	0.8		2	RInsol	23
3-[1-4-Cyano-1,2,3,4-tetrahydronapthyl)]propanenitrile	57964–40–6	4	Moderate	Impm	Freq	1	Low	1.6		3	Rsol	25
40-Crown-8	64001–04–3	4	Moderate	ImpM	Freq	2	Low	900		4	Soluble	30
30-Crown-6	64001–05–4	5	Moderate	ImpM	Freq	2	Low	78,000		4	Soluble	34
Tinuvin 622	65447–77–0	3	Low	Ingm	Freq	3	Mod	1,600		4	Soluble	29
35-Crown-7	66055–34–3	5	Moderate	ImpM	Freq	2	Low	180,000		4	Soluble	34
Nonylphenol-PEGylated	68412–54–4	2	Low	Impm	Freq	1	Low	> 10		4	Soluble	19
Alkylphenone	71868–10–5	3	Low	Impm	Freq	1	Low	280,000	500	4	Soluble	23
Diphenyl-(2,4,6-trimethyl-benzoly) phosphine oxide	75980–60–8	4	Moderate	Impm	Freq	1	Low	11		4	Soluble	27
Tridecanol/Decanylphenol-PEGylated	78330–21–9	3	Low	Impm	Freq	1	Low	> 10		4	Soluble	23
Atmer 163	107043–84–5	4	Moderate	Ingm	Freq	3	Mod	0.01		1	Insol	27
Polycup 1884	129807–53–0	5	Moderate	Ingm	Freq	3	Mod	> 10		4	Soluble	37
1-Propene-1,2,3-tricarboxylic acid, tributyl ester	343599–72–4	2	Low	Impm	Freq	1	Low	34		4	Soluble	19

Total Risk Score

Ultimately, a Total Risk Score for each extractable was calculated as a mathematical combination of the individual safety, availability and solubility risk scores. Although multiplicative and additive combinations have been used for other risk classifications (for example [8–13]), these combinations are based on an equal weighting of the individual risk factors. Since the focus of this process is safety risk estimation, the safety hazard score has a higher weight than the other factors. Additionally, the availability score, which considers both total pool and frequency of occurrence, was

Table VI Compilation of risk data, group 2 extractables

Extractable's ID		Safety component		Availability component				Solubility component				Total
Name	CAS RN	Score	Rank	Level	Occurrence	Score	Rank	Solubility, mg/L		Score	Rank	Risk score
								pH 2	pH 10			
Pimaric acid	79–54–9	2	Low	Impm	Freq	1	Low	2	11,000	3	Rsol	17
2,4-Bis-(1,1dimethylethyl)phenol	96–76–4	1	Negligible	ImpM	Freq	2	Int	120		4	Soluble	18
9,10-Epoxyoctadecanoic acid, butyl ester	106–83–2	6	High	Impm	Freq	1	Low	0.19	2	2	Risol	31
Tetradecamethyl-cycloheptasiloxane	107–50–6	3	Low	ImpM	Freq	2	Int	> 10		4	Soluble	26
Tetradecamethylhexasiloxane	107–52–8	2	Low	ImpM	Freq	2	Int	2.5		3	Rsol	20
Tetraethylene glycol	112–60–7	0	Negligible	Impm	Freq	2	Int	1,000,000		4	Soluble	14
Octadecenoic acid, methyl ester	112–62–9	1	Negligible	Impm	Freq	1	Low	1.1		3	Rsol	13
Octadecadienoic acid, methyl ester	112–63–0	1	Negligible	Impm	Rare	0	Low	1.9		3	Rsol	10
2,3-Hydroxyoctadecanoic acid, propyl ester	123–94–4	2	Low	Impm	Rare	0	Low	3		3	Rsol	14
Nonanol	132–08–8	2	Low	ImpM	Freq	2	Int	390		4	Soluble	22
2,6-Di-tert-butyl-4-methoxyphenol	489–01–0	2	Low	ImpM	Common	3	Mod	64		4	Soluble	25
1,8-Octadecanoic acid	505–48–6	1	Negligible	ImpM	Freq	2	Int	19,000	1,000,000	4	Soluble	18
Eicosanoic acid	506–30–9	1	Negligible	ImpM	Freq	2	Int	0.001	5.3	2	Rinsol	14
2-Hydroxycyclohexanone	533–60–8	2	Low	Impm	Rare	0	Low	139,000		4	Soluble	16
Hexadecamethylheptasiloxane	541–01–5	4	Moderate	ImpM	Freq	2	Int	0.6		2	Rinsol	26
Decamethylcyclopentasiloxane	541–02–6	2	Low	ImpM	Freq	2	Int	0.6		2	Rinsol	18
Hexadecanoic acid, 2,3-dihydroxypropyl ester	542–44–9	1	Negligible	Impm	Freq	1	Low	12		4	Soluble	15
1-Acetyl-piperdine	618–42–8	3	Low	Impm	Freq	1	Low	240		4	Soluble	23
2,2-Diethoxyethanol	621–63–6	2	Low	Impm	Freq	1	Low	275,000		4	Soluble	19
Hexadecanoic acid, ethyl ester	628–97–7	0	Negligible	ImpM	Freq	2	Int	1.2		3	Rsol	12
Hexadecanamide	629–54–9	1	Negligible	ImpM	Freq	2	Int	3.3		3	Rsol	16
2-Hydroxyheptanoic acid	636–69–1	1	Negligible	Impm	Rare	0	Low	47,000	1,000,000	4	Soluble	12
1,4-Cyclohexanedione	637–88–7	2	Low	Impm	Rare	0	Low	86,000		4	Soluble	16
Methyl-10-oxohexadecanoate	689–69–0	1	Negligible	Impm	Freq	1	Low	23		4	Soluble	15
1-Ethyl terephthalate	713–57–5	3	Low	ImpM	Freq	2	Int	1,200	1,000,000	4	Soluble	26
1,6-Dioxacyclododecane-7,12-dione	777–95–7	1	Negligible	Impm	Freq	1	Low	46,000		4	Soluble	15
Caprolactam tetramer	865–14–5	2	Low	ImpM	Freq	2	Int	600,000		4	Soluble	22
1,4-Methylenecyclohexanemethanol	1004–24–6	2	Low	Impm	Rare	0	Low	140		4	Soluble	16
Dimethyloxydimethylsilane	1112–39–6	4	Moderate	Impm	Rare	0	Low	281,000		4	Soluble	24
Dodecanamide	1120–16–7	2	Low	ImpM	Freq	2	Inter	64		4	Soluble	22
Diisooctyl maleate	1330–76–3	1	Negligible	Impm	Rare	0	Low	100		4	Soluble	12
2,6-Di-tert-butyl-4-(3-hydroxypropyl) phenol	1620–98–0	4	Moderate	Impm	Freq	1	Low	26	1,200	4	Soluble	27
1-Piperidinecarboxylic acid, methyl ester	1796–27–6	5	Moderate	Impm	Rare	0	Low	14,000		4	Soluble	28
1,11-Undecanedioic acid	1852–04–6	1	Negligible	Impm	Rare	0	Low	1,800	999,000	4	Soluble	12

Table VI (continued)

Extractable's ID		Safety component		Availability component				Solubility component				Total
Name	CAS RN	Score	Rank	Level	Occurrence	Score	Rank	Solubility, mg/L		Score	Rank	Risk score
								pH 2	pH 10			
Nonanedioic acid, methylester	2104–19–0	1	Negligible	Impm	Rare	0	Low	3,400	999,000	4	Soluble	12
9,12-Octadecadienoic acid	2197–37–7	1	Negligible	ImpM	Freq	2	Inter	4.2	23,000	3	Rsol	16
Gylceryl linoleate	2277–28–3	2	Low	Impm	Rare	0	Low	9.9		3	Rsol	14
Methylsilanetriol	2445–53–6	2	Low	Impm	Freq	1	Low	154,000		4	Soluble	19
1-Piperidinemethanol	2494–10–2	5	Moderate	Impm	Freq	1	Low	1,000,000	373,000	4	Soluble	31
9-Oxononanoic acid	2553–17–5	3	Low	Impm	Rare	0	Low	29,000	1,000,000	4	Soluble	20
9,10-Epoxyoctanoic acid, methyl ester	2566–91–8	5	Moderate	ImpM	Freq	2	Inter	1.9		3	Rsol	32
9,12-Octadecadienoic acid, ethyl ester	2566–97–4	1	Negligible	ImpM	Freq	2	Inter	1.9		3	Rsol	16
2,6-Di-tert-butyl-4-methylene-2,5-cyclodexadiene-1-one	2607–52–5	4	Moderate	ImpM	Freq	2	Inter	5.2		3	Rsol	28
4-Piperidinopyridine	2767–90–0	3	Low	Impm	Freq	1	Low	999,000		4	Soluble	23
2,6-Bis-(1,1-dimethyl)-4-(1-piperidinylmethyl)-phenol	2773–49–1	5	Moderate	Impm	Rare	0	Low	42,000	58	4	Soluble	28
1-Piperdinecarbothic acid, s-methyl ester	3012–97–3	5	Moderate	Impm	Freq	1	Low	2,200		4	Soluble	31
2,6-Di-tert-butyl-4-(3-hydroxypropyl)phenol	3080–84–0	2	Low	ImpM	Freq	2	Inter	45		4	Soluble	22
1,7-Dihydroxyoctamethyl-tetrasiloxane	3,081–07–0	1	Negligible	Impm	Rare	0	Low	140		4	Soluble	12
delta-Nonalactone	3301–94–8	2	Low	Impm	Rare	0	Low	2,000		4	Soluble	16
9-Octadecenamide (Oleamide)	3322–62–1	2	Low	Ingm	Common	4	High	0.006		1	Insol	22
Nonaethylene glycol	3386–18–3	1	Negligible	ImpM	Freq	2	Inter	999,000		4	Soluble	18
Erythro-9,10-dihydroxystearic acid	3639–32–5	2	Low	ImpM	Freq	2	Inter	60	316,000	4	Soluble	22
1,5-Dihydrohexamethyl-trisiloxane	3663–50–1	2	Low	Impm	Freq	1	Low	1,300		4	Soluble	19
11-Eicosenoic acid, methyl ester	3946–08–5	1	Negligible	Impm	Rare	0	Low	0.27		2	Rinsol	8
1,1-Dihydroxydodecamethyl-pentasiloxane	4029–00–9	2	Low	Impm	Rare	0	Low	3.4		3	Rsol	14
1-Cyclohexan-1-ol	4065–81–0	2	Low	Impm	Rare	0	Low	23,000		4	Soluble	16
1,8,15,22,29,36-Hexaazacyclodo-tetracontane-2,7,16.21.30.35-hexone	4174–07–6	2	Low	Impm	Freq	1	Low	380,000		4	Soluble	19
1,8,15,22-Tetraazacyclo-octacosane-2,7,16,21-tetrone	4238–35–1	2	Low	Impm	Freq	1	Low	9,000		4	Soluble	19
1,8-Diazacyclotetradecane-2,7-dione	4266–66–4	2	Low	Impm	Freq	1	Low	18,000		4	Soluble	19
Octadecanoic acid, 2,3-dihydroxypropyl ester	4748–78–1	3	Low	Impm	Rare		Low	510		4	Soluble	20
2-Ethyl-1,3-hexanediol isomer	4780–68–1	4	Moderate	Impm	Rare	0	Low	6,100		4	Soluble	24
Pentaethylene glycol	4792–15–8	2	Low	Impm	Freq	1	Low	1,000,000		4	Soluble	19
Octaethylene glycol	5117–19–1	2	Low	Impm	Freq	1	Low	1,000,000		4	Soluble	19
Methyl-1,4-benzenedicarboxylic acid	5156–01–4	0	Negligible	Impm	Freq	1	Low	180	1,000,000	4	Soluble	11
1-(1-Piperdinyl)-ethanethione	5309–92–2	5	Moderate	Impm	Rare	0	Low	2,400		4	Soluble	28
Decaethylene glycol	5579–66–8	2	Low	ImpM	Freq	2	Inter	1,000,000		4	Soluble	22

Table VI (continued)

Extractable's ID		Safety component		Availability component				Solubility component				Total
Name	CAS RN	Score	Rank	Level	Occurrence	Score	Rank	Solubility, mg/L		Score	Rank	Risk score
								pH 2	pH 10			
Bisphenol A Tetrol[a]	5581–32–8	4	Moderate	Ingm	Freq	3	Mod	49		4	Soluble	33
Heptaethylene glycol	5617–32–3	0	Negligible	ImpM	Freq	2	Inter	1,000,000		4	Soluble	14
3-Hydroxy-1-phenyl-1-propanone	5650–41–9	2	Low	Impm	Rare	0	Low	11,000		4	Soluble	16
Caprolactam cyclic tetramer	5834–63–9	2	Low	ImpM	Freq	2	Low	40,000		4	Soluble	22
2-Hydroxyhexanoic acid	6064–63–7	1	Negligible	Impm	Rare	0	Low	780	7,570	4	Soluble	12
1,4,7-Trioxacyclotridecane-8,13-dione	6607–34–7	3	Low	ImpM	Freq	2	Inter	210,000		4	Soluble	26
Dodecaethylene glycol	9/6/6,790	2	Low	ImpM	Freq	2	Inter	1,000,000		4	Soluble	22
Undecaethylene glycol	6809–70–7	2	Low	ImpM	Freq	2	Inter	1,000,000		4	Soluble	22
1,9-Dihydroxydecamethyl-pentasiloxane	7445–36–5	2	Low	Impm	Freq	1	Low	20		4	Soluble	19
2-Ethyl-1,3-hexanediol isomer	10017–84–2	4	Moderate	Impm	Rare	0	Low	42		4	Soluble	24
9-Hexadecenoic acid	10030–73–6	1	Negligible	Impm	Rare	0	Low	10	510,000	4	Soluble	12
3-Dodecanol	10203–30–2	1	Negligible	Impm	Rare	0	Low	13		4	Soluble	12
Eicosenamide	10436–08–5	2	Low	ImpM	Freq	2	Inter	0.4		2	Rinsol	18
4-Hydroxycyclohexanone	13482–22–9	2	Low	Impm	Rare	0	Low	280,000		4	Soluble	16
Epoxyoctadecanoic acid	13980–07–9	6	High	ImpM	Freq	2	Int	3	17,000	3	Rsol	36
Trimethyl-(1-methyl-1-phenylethoxy) silane	14629–57–3	4	Moderate	Impm	Rare	0	Low	94		4	Soluble	24
Cyclohexanone-3-carboxylic acid	16205–98–4	2	Low	Impm	Rare	0	Low	48,000	999,000	4	Soluble	16
1,3-Benzenedicarboxylic acid, ethylester	18189–42–9	2	Low	Impm	Freq	1	Low	1,400	1,000,000	4	Soluble	19
Methylcylcohexyl silanediol	18295–72–2	2	Low	Impm	Freq	1	Low	2,400		4	Soluble	19
1,3-Diethyl-1,1,3,3-tetramethyldisiloxane	18420–09–2	2	Low	Impm	Freq	1	Low	360		4	Soluble	19
7-Oxohydroabietic acid	18684–55–4	1	Negligible	Impm	Rare	0	Low	4	19,000	3	Rsol	10
3,6,4,17-Tetraoxatricyclo-tetracosa-1,8,10,12,19,21-hexaene-2,7,13, 18-tetraone	18864–78–3	2	Low	Impm	Freq	1	Low	54		4	Soluble	19
Gylceryl monopalmitate	19670–51–0	2	Low	ImpM	Freq	2	Inter	12		4	Soluble	22
3-Ethyl-4-nonanol	19780–72–4	1	Negligible	Impm	Rare	0	Low	69		4	Soluble	12
Palmitic acid, 2-ethyl ester	22613–62–3	1	Negligible	1mpM	Freq	2	Inter	0.15		2	Rinsol	14
1,4-Benzenedicarboxylic acid, 1-[2-[[4-[(2-hydroxyethoxy)-carbonyl]benzoyl]oxy]ethyl] ester, PET linear dimer	23186–89–2	1	Negligible	ImpM	Freq	2	Inter	120	140,000	4	Soluble	18
1,4-Benzenedicarboxylic acid, 1,4-bis (4-hydroxy) butyl ester	23358–95–4	0	Negligible	ImpM	Freq	2	Inter	71		4	Soluble	14
cis-9,10-Epoxyoctadecanoic acid	24560–98–3	5	Moderate	Ingm	Freq	3	Mod	3	17,000	3	Rsol	35
Polyethylene glycol[a]	25322–68–3	2	Low	Ingm	Common	4	High	10,000		4	Soluble	28
Gylceryl monooleate	25496–72–4	2	Low	ImpM	Freq	2	Inter	6		3	Rsol	20
	34006–77–4	3	Low	ImpM	Freq	2	Inter	5.5		3	Rsol	24

Table VI (continued)

Extractable's ID		Safety component		Availability component				Solubility component				Total
Name	CAS RN	Score	Rank	Level	Occurrence	Score	Rank	Solubility, mg/L		Score	Rank	Risk score
								pH 2	pH 10			
1,2-Benzenedicarboxylic acid, ethylmethyl ester												
9-Oxononanoic acid, 1-methylethyl ester	34208–02–1	3	Low	Impm	Rare	0	Low	300		4	Soluble	20
3,5-(1,1-Dimethylethyl)-4-hydroxy-benzenepropanol	36294–23–2	2	Low	Impm	Rare	0	Low	95		4	Soluble	16
10-Oxoundecanoic acid, ethyl ester	36651–38–4	1	Negligible	Impm	Freq	1	Low	430		4	Soluble	15
Heptanol	53535–33–4	2	Low	ImpM	Freq	2	Inter	1,800		4	Soluble	22
Caprolactam cyclic dimer	56403–09–9	2	Low	ImpM	Freq	2	Inter	92		4	Soluble	22
1,2,4-Benzenetricarboxylic acid, 2-(2-ethylhexyl) ester	63468–08–6	2	Low	ImpM	Freq	2	Inter	23	130,000	4	Soluble	22
1,2,4-Benzenetricarboxylic acid, 1,2-bis (2-ethylhexyl) ester	63468–09–7	3	Low	Impm	Rare	0	Low	0.12	120	3	Rsol	18
1,4,11,14-Tetraoxacy-cloeicosane-5,10,15,20-tetrone	64066–17–7	1	Negligible	Impm	Freq	1	Low	344,000		4	Soluble	15
Ethoxydimethylsilanol	65007–35–4	2	Low	Impm	Freq	1	Low	26,000		4	Soluble	19
Heptabutylene glycol	68936–03–8	3	Low	Impm	Freq	1	Low	3,900		4	Soluble	23
Bis-(2,4-di-tert-butylphenyl)phosphate	69284–93–1	3	Low	ImpM	Freq	2	Inter	240	14,000	4	Soluble	26
13(Z)-Docosenenitrile	73170–89–5	2	Low	Impm	Rare	0	Low	0.013		0	Insol	8
4-Oxononanal	74327–29–0	3	Low	Impm	Rare	0	Low	2,500		4	Soluble	20
Octabutylene glycol	77920–52–6	3	Low	Impm	Rare	0	Low	3,500		4	Soluble	20
Octadecanoic acid, 2,3-dihydroxypropyl ester	78837–87–3	1	Negligible	ImpM	Freq	2	Inter	100,000		4	Soluble	18
1-Oxaspiro[4.5]deca-6,9-diene-2,8-dione, 7,9-bis (1,1-dimethylethyl)-	82304–66–3	5	Moderate	ImpM	Common	3	Mod	280		4	Soluble	37
2,5-Cyclohexadiene-1-propanoic acid, 3,5-bis(1,1 -dimethylethyl)-1-hydroxy-4-oxo-	83237–15–4	3	Low	ImpM	Common	3	Mod	880	1,000,000	4	Soluble	29
2,(2-(2-Hydroxyethoxy)ethoxy)-acetic acid, methyl ester	86520–57–2	1	Negligible	Impm	Rare	0	Low	996,000		4	Soluble	2
1,5-Dioxacyclopentadecane-6,15-dione, 3,3-di-methyl-	94113–50–5	1	Negligible	Impm	Freq	1	Low	5,100		4	Soluble	15
9,10-Epoxyoctadecanoic acid, isopropyl ester	95007–80–0	4	Moderate	ImpM	Freq	2	Inter	0.4		2	Rinsol	26
Tris(2,4-di-tert-butylphenyl) phosphate	95906–11–9	3	Low	ImpM	Freq	2	Inter	0.001		0	Insol	18
1,2-Benzenedicarboxylic acid, 1-octyl-2-pentyl ester	102148–90–3	6	High	Impm	Freq	1	Low	0.7		2	Rinsol	31
13-Hexyloxacyclotri-dec-10-ene-2-one	127062–51–5	1	Negligible	Impm	Rare	0	Low	25		4	Soluble	12
9,10-dihydroxy-12,13-epoxy stearic acid	127105–40–2	6	High	ImpM	Freq	2	Inter	83	440,000	4	Soluble	38
3-(2,3-Dihydroxyoctyl)-2-oxiraneoctanoic acid	127105–41–3	6	High	Impm	Freq	1	Low	83	440,000	4	Soluble	
1,4-Benzenedicarboxylic acid, 4-hydroxybutyl 2-hydroxyethyl ester	854985–22–1	0	Negligible	Impm	Freq	1	Low	2,800		4	Soluble	11

Table VII Compilation of risk data, group 3 extractables

Extractable's ID		Safety component		Availability component				Solubility component				Total risk score
Name	CAS RN	Score	Rank	Level	Occurrence	Score	Rank	Solubility, mg/L		Score	Rank	
								pH 2	pH 10			
N-Ethyl-4-methyl-benzene-sulfonamide	80–39–7	3	Low	Impm	Common	2	Inter	1,900		4	Soluble	26
Hydroxystearic acid	106–14–9	3	Low	Impm	Freq	1	Low	20	110,000	4	Soluble	23
2,5-Dimethyl-2,5-hexanediol	110–03–2	3	Low	ImpM	Freq	2	Inter	13,000		4	Soluble	26
9,10-Dihydroxyoctadecanoic acid	120–87–6	2	Low	Impm	Freq	1	Low	60	316,000	4	Soluble	19
4-(1,1,3,3-tetramethylbutyl)-phenol	140–66–9	1	Negligible	Impm	Rare	0	Low	62	110	4	Soluble	12
Dihydro-5-tetradecyl-2(3H)-furanone	502–26–1	2	Low	ImpM	Freq	2	Inter	1.9		3	Rsol	20
2-Hydroxy-2-methylpropanoic acid	594–61–6	3	Low	Impm	Rare	0	Low	507,000	1,000,000	4	Soluble	20
5-Nonanol	623–93–8	2	Low	Impm	Rare	0	Low	550		4	Soluble	16
Methylenebutanedioic acid, dimethyl ester	617–52–7	1	Negligible	Impm	Rare	0	Low	33,000		4	Soluble	12
4-Ethoxybenzoic acid	619–86–3	2	Low	Impm	Freq	1	Low	1,700	1,000,000	4	Soluble	19
10-Oxo-hexanoic acid, methyl ester	628–97–7	1	Negligible	Impm	Freq	1	Low	1.2		3	Rsol	13
1-[4-(1-Methylethyl)phenyl] ethanone	645–13–6	1	Negligible	Impm	Rare	0	Low	260		4	Soluble	12
5-Amino-2-cyanobenzotrifluoride	654–70–6	6	High	Impm	Freq	1	Low	280		4	Soluble	35
Palmitic acid, ethyl ester	689–69–0	1	Negligible	Ingm	Freq	3	Mod	23		4	Soluble	21
Bicyclo[4.2.0]octa-1,3,5-triene	694–87–1	2	Low	Impm	Rare	0	Low	56		4	Soluble	16
10-Oxooctadecanoic acid, methyl ester	870–10–0	1	Negligible	Impm	Freq	1	Low	5.6		3	Rsol	13
1,4-Diphenyl-1,3-butadiene	886–65–7	3	Low	Impm	Rare	0	Low	1.6		3	Rsol	18
2-Methoxy-2-phenyl propane	935–67–1	2	Low	Impm	Rare	0	Low	1,700		4	Soluble	16
2(3H)-Benzothiazole	934–34–9	3	Low	Ingm	Freq	3	Mod	670	920	4	Soluble	29
Bis-(2-hydroxyethyl terephthalate)	959–26–2	1	Negligible	ImpM	Freq	2	Inter	11,000		4	Soluble	18
1,3-(1,1-dimethylethyl)-benzene	1014–60–4	1	Negligible	Impm	Rare	0	Low	0.009		0	Insol	4
N-Ethyl-2-methyl-benzenesulfonamide	1077–56–1	3	Low	Impm	Common	2	Inter	2,200		4	Soluble	26
9,10-Dihydroxyoctadecanoic acid, methylester	1115–01–1	2	Low	ImpM	Freq	2	Inter	27		4	Soluble	22
1-Hydroxycyclohexane-carboxylic acid	1123–28–0	3	Low	Impm	Rare	0	Low	140,000	1,000,000	4	Soluble	20
Mono-2-hydroethylterephthalate	1137–99–1	1	Negligible	ImpM	Freq	2	Inter	16,000	1,000,000	4	Soluble	18
Octadecanoic acid, hexadecyl ester	1190–63–2	1	Negligible	ImpM	Freq	2	Inter	0.001		0	Insol	10
2-Hexenoic acid	1191–04–4	3	Low	Impm	Rare	0	Low	4,800	1,000,000	4	Soluble	20
5-Hydroxy-octadecanoic acid, 8-lactone	1227–51–6	1	Negligible	Impm	Rare	0	Low	26		3	Rsol	10
1,1,1-Trimethyl-2,2,2-triphenyl disilane	1450–18–6	4	Moderate	Impm	Rare	0	Low	0.04		0	Insol	16
4-Hydroxy-3-pentene-2-one	1522–20–9	7	High	Impm	Freq	1	Low	24,000	960,000	4	Soluble	39
Methylbutanedioic acid, dimethyl ester	1604–11–1	3	Low	Impm	Rare	0	Low	26,000		4	Soluble	20
9,10-Dihydroxyhexadecanoic acid	1747–02–0	2	Low	ImpM	Freq	2	Inter	1,100	1,000,000	4	Soluble	22
Carbonic acid, dipentyl ester	2050–94–4	1	Negligible	Impm	Rare	0	Low	180		4	Soluble	12
9-Hexadenenoic acid	2091–29–4	2	Low	Impm	Freq	1	Low	10	51,000	4	Soluble	19
2-Hydroxy-2-methylpropanoic acid, methyl ester	2110–78–3	5	Moderate	Impm	Freq	1	Low	203,000		4	Soluble	31
2,4-Dimethylpentanedioic acid, dimethyl ester	2121–68–8	2	Low	Impm	Rare	0	Low	7,000		4	Soluble	16
Linear polyethylene terephthalate dimer	2144–69–6	1	Negligible	Impm	Freq	1	Low	100		4	Soluble	15
Terephthalic acid, ethylene ester	2225–05–0	3	Low	Impm	Freq	1	Low	50	502,000	4	Soluble	23
2-Hexen-1-ol	2305–21–7	1	Negligible	Impm	Rare	0	Low	14,000		4	Soluble	12
9-Oxononanoic acid	2553–17–5	3	Low	impM	Freq	2	Inter	2,900	1,000,000	4	Soluble	26
Oxahexanoic acid, methyl ester	2955–62–6	2	Low	impm	Freq	1	Low	30,000		4	Soluble	19
1-Methylsulfinyldodecane	3079–30–9	4	Moderate	Impm	Rare	0	Low	350		4	Soluble	24
1-Cyclohexene-1-ethanol	3197–68–0	2	Low	Impm	Rare	0	Low	8,300		4	Soluble	16
Erythro-9,10-dihydroxyoctadecanoic acid	3639–32–5	2	Low	Impm	Freq	1	Low	60	316,000	4	Soluble	19

Table VII (continued)

Extractable's ID		Safety component		Availability component				Solubility component				Total risk score
Name	CAS RN	Score	Rank	Level	Occurrence	Score	Rank	Solubility, mg/L		Score	Rank	
								pH 2	pH 10			
1,1-Diethoxypentane	3658–79–5	1	Negligible	Impm	Freq	1	Low	5,400		4	Soluble	15
1,1-Diethyoxyhexane	3658–93–3	1	Negligible	Impm	Freq	1	Low	2,600		4	Soluble	15
Dibutyl silanediol	3959–09–9	3	Low	Impm	Freq	1	Low	630		4	Soluble	23
Tributyleneglycol	4161–33–5	1	Negligible	ImpM	Freq	2	Int	45,000		4	Soluble	18
2-Phenyl-1,2-propane diol	4217–66–7	2	Low	ImpM	Freq	2	Inter	230,000		4	Soluble	22
9,10-Dihydroxyoctadecanoic acid, ethyl ester	4277–20–7	2	Low	ImpM	Freq	2	Inter	13		4	Soluble	22
2-Methyl-5-methylenehexanoic acid, dimethyl ester	4513–62–6	3	Low	Impm	Rare	0	Low	4,400		4	Soluble	20
Octadecanoic acid, dodecyl ester	5303–25–3	1	Negligible	Impm	Freq	1	Low	0.001		0	Insol	7
Heptadecanenitrile	5399–02–0	3	Low	Impm	Rare	1	Low	1.1		3	Rsol	21
Benzoic acid, 2-ethylhexyl ester	5444–75–7	3	Low	ImpM	Freq	2	Inter	14		4	Soluble	26
2,4-Dimethyl-4-nitro-pentanoic acid, methyl ester	5762–40–3	5	Moderate	Impm	Rare	0	Low	8,700		4	Soluble	28
Dimethylbenzaldehyde	5779–95–3	3	Low	Impm	Freq	1	Low	340			Soluble	23
3-Hydroxy-4-methyl-pentanoic acid	5980–21–2	4	Moderate	Impm	Rare	0	Low	12,000	1,000,000	4	Soluble	24
Lauryl lactate	6283–92–7	1	Negligible	ImpM	Freq	2	Inter	88		4	Soluble	18
1-Octadecyl ether	6297–03–6	2	Low	Impm	Rare	0	Low	<0.001		0	Insol	8
n-Heptyl hexanoate	6976–72–3	2	Low	Impm	Rare	0	Low	43		4	Soluble	16
2-Butanedioc acid, 1,4-bis(2-hydroxypropyl) ester	10095–17–7	1	Negligible	Impm	Rare	0	Low	650,000		4	Soluble	12
Nitropentanoic acid, methyl ester	10312–37–5	4	Moderate	Impm	Rare	0	Low	210	1,000,000	4	Soluble	24
2,4-Dimethyl-5-oxo-pentanoic acid, methyl ester	10348–62–6	4	Moderate	Impm	Rare	0	Low	6,200		4	Soluble	24
4,4,6-Trimethyl-2-cyclohexen-1-one	13395–73–8	4	Moderate	Impm	Rare	0	Low	3,500		4	Soluble	24
4-Hydroxyhexanoic acid	13532–38–2	2	Low	Impm	Rare	0	Low	120,000	1,000,000	4	Soluble	16
3-Ethylheptanoic acid	14272–47–0	2	Low	Impm	Rare	0	Low	1,100	1,000,000	4	Soluble	16
4-Methoxy-3-methylphenol	14786–82–4	4	Moderate	Impm	Rare	0	Low	5,100	6,500	4	Soluble	24
1,4-Benzenedicarboxylic acid, 1-[2-[(4-carboxybenzoyl)-oxy]-ethyl]-4-[2-[[4-[(2-hydroxy-ethoxy)-carbonyl] benzoyl]-oxy]ethyl] ester (PET linear trimer)	16958–96–6	1	Negligible	ImpM	Freq	2	Inter	1.6	1,900	3	Rsol	16
Octadecanoic acid, tetradecyl ester	17661–50–6	1	Negligible	Impm	Rare	0	Low	<0.001		0	Insol	4
3-Ethoxy-1,1,1,5,5,5-hexamethyl-3-(trimethyl-siloxy) trisiloxane	18030–67–6	4	Moderate	Impm	Rare	0	Low	17		4	Soluble	24
Eicosanoic acid, ethyl ester	18281–05–5	1	Negligible	Impm	Rare	0	Low	<0.001		0	Insol	4
Dicyclohexylmethylsilanediol	18295–72–2	4	Moderate	Impm	Freq	1	Low	2,400		4	Soluble	27
3,4-Dimethyl-3-hexanol	19550–08–4	5	Moderate	Impm	Freq	1	Low	3,100		4	Soluble	31
2,5-Dimethyl-2-hexenedioic acid, dimethyl ester	19550–59–5	3	Low	Impm	Rare	0	Low	5,200		4	Soluble	20
2,3-Octanediol	20653–90–1	2	Low	Impm	Freq	1	Low	5,000		4	Soluble	19
1,2,3,5-Bis-O-(1-methyl-ethylidene)-alpha-D-xylofuranose	20881–04–3	3	Low	Impm	Rare	0	Low	2,000		4	Soluble	20
Tetradecanoic acid, 2-hydroxyethyl ester	22122–18–5	1	Negligible	Impm	Rare	0	Low	41		4	Soluble	12
Methylethyl terephthalate	22163–52–6	2	Low	ImpM	Freq	2	Low	670		4	Soluble	22
t-Butyl-3-hydroxybutyl ether	22419–28–9	2	Low	Impm	Rare	0	Low	15,000		4	Soluble	16
3(p-Hydroxyphenyl)-lactic acid	23508–35–2	1	Negligible	Impm	Rare	0	Low	150,000	1,000,000	4	Soluble	12
6-Undecanol	23708–56–7	2	Low	Impm	Rare	0	Low	48		4	Soluble	16
Octanoic acid, 2-hydroxypropyl ester	23794–30–1	2	Low	Impm	Rare	0	Low	1,900		4	Soluble	16
Citraconic acid, bis-(2-hydroxypropyl) ester	24429–30–9	2	Low	Impm	Rare	0	Low	42,000		4	Soluble	16

Table VII (continued)

Extractable's ID		Safety component		Availability component				Solubility component				Total risk score
Name	CAS RN	Score	Rank	Level	Occurrence	Score	Rank	Solubility, mg/L		Score	Rank	
								pH 2	pH 10			
8,11-Dimethyl-2,9,10-trioxa-6-azonia-1-boratatricyclo-[4.33.0(1,60]-dodecane	27664–58–0	5	Moderate	Impm	Freq	1	Low	> 10		4	Soluble	31
9,10-Dihydroxyhexadecanoic acid	29242–09–9	2	Low	ImpM	Freq	2	Inter	250	1,000,000	4	Soluble	22
9,10-Dihydroxyocta-decanedioic acid, monoethyl ester	31535–15–6	3	Low	Impm	Rare	0	Low	110	57,300	4	Soluble	20
2-Hydroxypropyl acrylate	32029–53–1	4	Moderate	Impm	Rare	0	Low	450,000		4	Soluble	24
Poly[imino(1,6-dioxo-1,6-hexanediyl) imino-1,6-hexanediyl] (Nylon 66 hexamer)	32131–17–2	5	Moderate	IngM	Freq	4	High	<0.1		0	Insol	32
2-Hydroxy-2-methylbutanoic acid, methyl ester	32793–34–3	5	Moderate	Impm	Rare		Low	93,000		4	Soluble	28
2,4-Dimethyl-4-pentenoic acid, methyl ester	34998–29–3	4	Moderate	Impm	Rare	0	Low	4,700		4	Soluble	24
10-Oxo-undecanoic acid, ethyl ester	36651–38–4	1	Negligible	Impm	Rare	0	Low	430		4	Soluble	12
4-Hexyloxyphenyl-4′-hexyloxybenzoate	38454–31–8	3	Low	Impm	Rare	0	Low	<0.1		0	Insol	12
Chlorodimethylsilanol	44127–81–3	4	Moderate	Impm	Rare	0	Low	49,000		4	Soluble	24
Nonanoic acid, butyl ester	50623–57–9	1	Negligible	Impm	Rare	0	Low	43		4	Soluble	12
2,4,6-Trimethyl-1,3,5-cyclohexanetricarboxylic acid	54120–00–2	1	Negligible	Impm	Rare	0	Low	990		4	Soluble	12
4-Tetradecane	54322–28–0	1	Negligible	Impm	Rare	0	Low	<0.1		0	Insol	4
1,1-Diethoxynonane	54815–13–3	1	Negligible	Impm	Rare	0	Low	280		4	Soluble	12
1-Phenyl-1,3,5-hexatriene	54826–11–8	3	Low	Impm	Rare	0	Low	12		4	Soluble	20
1,1-Diethoxyoctane	54889–48–4	1	Negligible	Impm	Rare	0	Low	590		4	Soluble	12
1,3-Dimethyl-3-butenyl-benzene	56851–51–5	2	Low	Impm	Rare	0	Low	5.1		3	Rsol	14
2-[1-(4-Cyano-1,2,3,4- tetra-hydronapthyl)]propanenitrile	57964–39–3	4	Moderate	Impm	Freq	1	Low	0.82		2	Rinsol	23
2-[1-(4-Cyano-1,2,3,4- tetra-hydronapthyl)]propanenitrile	57964–40–6	4	Moderate	Impm	Freq	1	Low	1.6		3	Rsol	25
1,4,7-Trioxacyclotridecane-8,13-dione	58984–19–3	3	Low	ImpM	Freq	2	Inter	400,000		4	Soluble	26
Tetrabutyleneglycol	61136–07–0	1	Negligible	ImpM	Freq	2	Inter	18,000		4	Soluble	18
Pentabutyleneglycol	61136–08–1	1	Negligible	ImpM	Freq	2	Low	9,100		4	Soluble	18
Terephthalic acid, methyl-2-ethylhexyl ester	63468–13–3	5	Moderate	Impm	Freq	1	Low	76		3	Rsol	29
9,10-Dihydroxyoctadecanoic acid, 1,18-dimethyl ester	67852–29–3	2	Low	Impm	Freq	1	Low	100		4	Soluble	19
Hexabutyleneglycol	68936–02–7	3	Low	ImpM	Freq	2	Inter	5,400		4	Soluble	26
2,4-Dimethyl-heptanedioic acid, dimethyl ester	72719–04–1	3	Low	Impm	Rare	0	Low	1,800		4	Soluble	20
4-Oxononanal	74327–29–0	4	Moderate	Impm	Freq	1	Low	2,500		4	Soluble	27
2-Methyl-2,2-dimethyl-1-(2-hydroxy-1-methylethyl) propyl propanoate	74367–33–2	3	Low	Impm	Rare	0	Low	1,800		4	Soluble	20
2-Methyl-3-hydroxy-2,4,4-trimethy lpentyl propanoate	74367–34–3	3	Low	Impm	Rare	0	Low	1,800		4	Soluble	20
Diisobutyric acid, 1-tert-butyl-2-methyl-1,3 propanediyl ester	74381–40–1	3	Low	Impm	Rare	0	low	60		4	Soluble	20
2-Methyl-3-methylene-cyclopentene-carboxylic acid, methyl ester	74764–25–3	1	Negligible	Impm	Freq	1	Low	830		4	Soluble	15
2,4,5,6,7,7a-hexahydro-4,4,7a-trimethyl-cis-benzofuran-methanol	77384–15–7	5	Moderate	Impm	Rare	0	Low	2,600		4	Soluble	28
trans-1,2-Cyclopentane-dicarboxylic acid, dimethyl ester	941–75–3	1	Negligible	Impm	Rare	0	Low	780		4	Soluble	12
N-(1-cyano-1-methylethyl)iso-butyramide	84213–57–0	3	Low	Impm	Rare	0	Low	11,000		4	Soluble	20
2-(Hexyloxy)-N,N-dipropyl acetamide	86520–57–2	3	Low	ImpM	Freq	2	Inter	996,000		4	Soluble	26

Table VII (continued)

Extractable's ID		Safety component		Availability component				Solubility component				Total risk score
Name	CAS RN	Score	Rank	Level	Occurrence	Score	Rank	Solubility, mg/L		Score	Rank	
								pH 2	pH 10			
3-Methyl-2,4-octadienoic acid, methyl ester	91057–12–4	1	Negligible	Impm	Rare	0	Low	1,200		4	Soluble	12
4-(Hydroxymethyl)-cyclohexane-carboxaldehyde	92385–32–5	3	Low	Impm	Freq	1	Low	20,000		4	Soluble	23
Carbonic acid, propyl ester diester with 1,4-butanediol	96620–38–1	3	Low	Impm	Rare	0	Low	520		4	Soluble	20
Cyclopentane carboxylic acid, octyl ester	100912–19–4	3	Low	Impm	Freq	1	Low	25		4	Soluble	23
2-Hydroxydecanedioic acid	103963–71–9	4	Moderate	Impm	Freq	1	Low	34,000	1,000,000	4	Soluble	27
Hexenoic acid, methyl ester	113118–53–9	2	Low	Impm	Rare	0	Low	6,500		4	Soluble	16
Heptadecene-7,10-dione	120090–98–4	3	Low	Impm	Freq	1	Low	26		4	Soluble	23
5-Hydroxy-2-methyl-3-hexenoic acid, methyl ester	123061–22–3	1	Negligible	Impm	Rare	0	Low	51,000		4	Soluble	12
Terephthalic acid, ethyl 2-ethylhexyl ester	155603–50–2	2	Low	Impm	Freq	1	Low	18,000		4	Solule	19
1-Cyclooctene-1,2-diol	722553–47–1	3	Low	Impm	Rare	0	Low	6,300		4	Soluble	20
Dihydroxymyristic acid	726173–79–1	3	Low	Impm	Freq	1	Low	1,100	1,000,000	4	Soluble	23
Cyclopentene carboxylic acid, heptadecyl ester	959257–10–4	5	Moderate	Impm	Rare	0	Low	0.04		0	Insol	20
2-Methyl-4-phenyl butyric acid, methyl ester	1000194–68–9	2	Low	Impm	Rare	0	Low	6,600		4	Soluble	16

weighted higher than the solubility score, which is based on a single input. Considering these weightings, the Total Risk Score was calculated as follows (Table IV):

$$\text{Total Risk Score(TRS)} = 4 \times (\text{safety hazard}) + 3 \times (\text{availability score}) + 2 \times (\text{solubility score})$$

Thus a higher TRS corresponds to a greater risk. While the assignment of the weighting factors may be construed to be arbitrary, these values were chosen in the context of establishing Safety Risk Categories, as follows. Specifically, the use of the factors 4, 3 and 2 produced a TRS scale that was sufficiently broad that the extractables could be effectively categorized but not so broad that the distribution of the extractables within the risk categories was distorted by having too many possible TRS values.

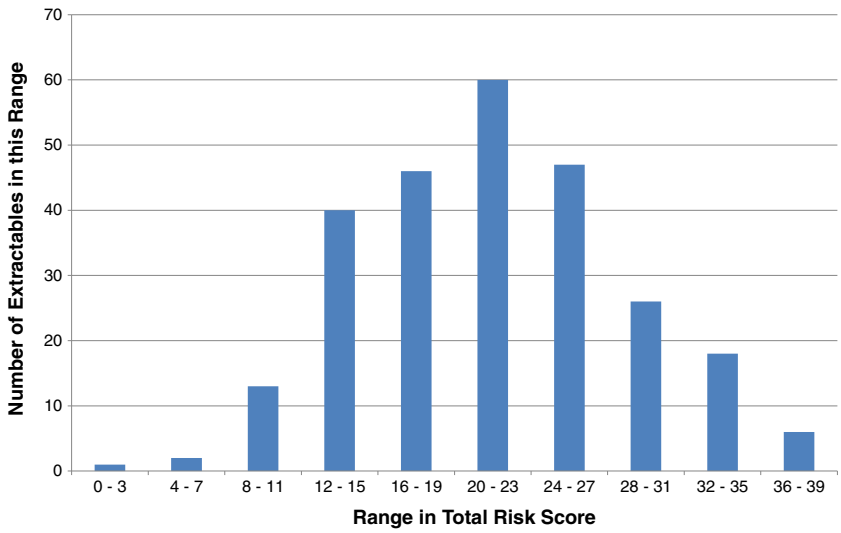

Fig. 2 Distribution of the total risk scores (TRS) for the approximately 500 Extractables considered in this study. The total risk scores are normally distributed around a TRS value of 20–23, corresponding to the transition between the moderate and intermediate risk categories. Summary statistics associated with the distribution of the TRS values are contained in Table VIII.

Table VIII Statistical analysis of the total risk score data

Statistical Property	Value for extractables group			
	Group 1 ($n = 245$)	Group 2 ($n = 125$)	Group 3 ($n = 136$)	All ($n = 506$)
Mean	21.8	19.8	19.3	20.7
Standard deviation	7.1	6.5	6.4	6.9
Median	22	19	20	20
Mode	23	22	20	23

Safety Risk Categories

The primary purpose of establishing the Risk Evaluation Matrix and using the Matrix to assign Total Risk Scores to individual extractables is the distribute the population of extractables into discrete Safety Risk Categories, based on the risk that the extractable would adversely affect patient safety as a leachable if a packaging system, manufacturing system or drug delivery device was constructed from a material that could contain the extractable. To accomplish this objective, four Safety Risk Categories were created, corresponding to lowest risk, moderate risk, intermediate risk and highest risk. These somewhat generic descriptors for the Safety Risk Categories were made more concrete by specifying those Total Risk Scores that establish the boundaries of the Risk Categories (see Table IV). Thus for example, the lowest risk category was established to include all those extractables whose safety hazard was low (corresponding specifically to safety hazard scores or 2 or less), whose availability was low (availability score of 1 or less) and whose solubility was low (classified as insoluble, solubility score of 1). Clearly, these individual scores were chosen to reflect extractables that represent a low safety risk. Using the previously defined TRS equation, the upper limit of Total Risk Scores for the lowest risk category becomes 4(2) + 3(1) + 1 (1) = 13. Thus extractables with a TRS of 13 or less are classified as lowest risk.

Similar calculations for the boundaries in the other three categories are shown in Table IV. For example, an extractable in the highest risk category is one whose safety hazard was high (score of 5 or higher), whose availability was high (Availability score of 4 or higher), and which was highly soluble (solubility score of 4).

RESULTS

The individual Total Risk Scores for approximately 500 extractables are contained in Tables V, VI and VII. These extractables are a subset of extractables which

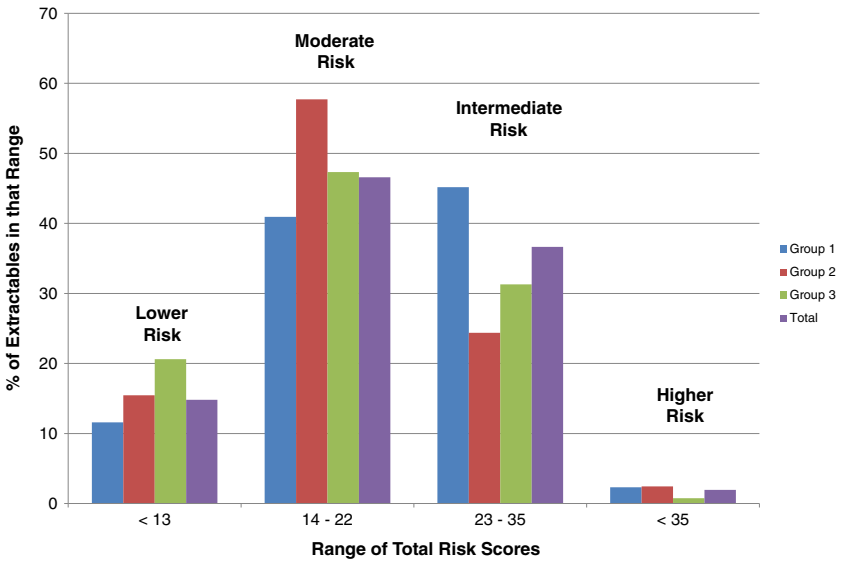

Fig. 3 Distribution of the total risk scores as a function of Extractables Groups. The entire population of extractables was broken up into three groups as a function of the availability of toxicological data. Extractables in Group 1 had available and adequate toxicological data, extractables in Groups 2 and 3 did not have such data and were safety assessed using surrogate compounds. In Group 2, the surrogate was another extractable from Group 1; in Group 3 the surrogate was not an extractable but merely a structural mimic. Although there are no readily discernible differences in the distributions as a function of extractable's Group, Group 1 extractables are more frequently encountered in the higher risk categories.

Table IX Extractables in the highest risk cetegory

Extractable	CAS RN	Total Risk score	Discussion
Dibenzyl amine	103–49–1	39	Cramer Class 3 with no in vitro mutagencity data, lower RI value. Frequently observed within a material class, occasionally as a major ingredient. Highly soluble.
9,10-Epoxystearic acid	2443–39–2	39	Cramer Class 3 with no invitro mutagencity data and insilico mutagencity alert, lower RI value. Frequently observed within a material class, typically as a minor ingredient. Relatively soluble
4-Hydroxy-3-pentane-2-one	1522–20–9	39	Cramer Class 3 with no invitro mutagencity data and insilico mutagencity alert, much lower RI value. Frequently observed within a material class, typically as a minor ingredient. Highly soluble
Benzaldehyde	100–52–7	38	Much lower RI value, both in vitro and in silico mutagencity alerts. Frequently observed within a material class, typically as a major impurity. Highly soluble.
Acrylonitrile	107–13–1	38	Cramer Class 3 with in vitro mutagencity alert, very low RI value. Frequently observed within a material class, as a minor impurity. Highly soluble.
Monoethyl phthalate	2306–33–4	38	Cramer Class 3 with no invitro mutagencity data and insilico mutagencity alert, lower RI value. Frequently observed within a material class, typically as a minor impurity. Highly soluble.
9,10-dihydroxy-12, 13-epoxystearic acid	127105–40–2	38	Cramer Class 3 with no invitro mutagencity data and insilico mutagencity alert, lower RI value. Frequently observed within a material class, occasionally as a major impurity. Highly soluble.
Poly Cup 1884	129807–53–0	37	Cramer Class 3, no invitro and in silico mutagencity data, lower RI value. Frequently observed within a material class, occasionally as a minor ingredient. High solubility.
1-Oxaspiro[4.5]deca-6,9-diene-2,8-dione, 7,9-bis(1,1-dimethylethyl)-	82304–66–3	37	Cramer Class 3 with no invitro mutagencity data and insilico mutagencity alert, moderate RI value. Commonly observed across material classes, typically as a minor impurity. Highly soluble.
Epoxy octadecanoic acid	13980–07-9	36	Cramer Class 3 with no invitro mutagencity data and insilico mutagencity alert, lower RI value. Frequently observed within a material class, occasionally as a major impurity. Highly soluble

had been previously assessed for their potential to adversely impact patient safety [2]. Only a subset of the previously-evaluated database was appropriate for use in this assessment as the required information (such as aqueous solubility) was not available for all the members of the previous data set. As noted in the previous assessment, the extractables were initially divided into three groups depending on the availability and rigor of the available toxicological information used to establish the safety score, with Group 1 extractables representing those extractables whose available toxicological information was sufficiently robust to directly assess the safety hazard and Groups 2 and 3 representing those extractables which did not have sufficiently useful toxicological information to directly assess the safety hazard. For those substances in Groups 2 and 3, toxicological information was inferred using structurally similar surrogate substances that possessed sufficiently useful toxicological data, with Group 2 extractables having surrogates that themselves were Group 1 extractables and Group 3 extractables having surrogates which were not extractables themselves. Tables V through VII include the assigned values of the various safety-indicating parameters, the qualitative descriptors associated with the score for each safety-indicating parameter and the Total Risk Score.

A frequency distribution plot for the Total Risk Scores is shown in Fig. 1. Summary statistics such as the means, median and mode of the Total Risk Scores are contained in Table VIII.

Figure 2 illustrates the distribution of the extractables in the four Safety Risk classes as a function of the extractable's Group designation. Although the scale of TRS values extends from 0 to 55, the highest TRS obtained for any extractable was 39. The distribution of the Total Risks Scores is generally normal (Fig. 1), centered on a TRS score of approximately 20, which corresponds to a classification of moderate risk. The mean, mode and median TRS values were all in the range of 19 to 23 (Table VIII) and there was no meaningful difference in the distribution profiles between the extractable's Groups. The region defined by the mean plus or minus one standard deviation encompasses nearly the entire region of moderate and intermediate risk. The disproportionally large group of extractables with a TRS value of 12 represents compounds which (1) have generally low associated toxicity, (2) are rarely encountered in materials in potentially meaningful quantities (leading to a lower TRS), and (3) which are highly soluble (contributing to a higher TRS value). Numerous extractables shared these fairly common general characteristics and their associated Total Risk Score.

The ten extractables that have been classified into the Highest Risk category are summarized in Table IX. At the other end of the spectrum, the seventy-eight extractables that fall within the Lowest Risk category are summarized in Table X.

Table X Extractables in the lower risk category

Extractable	CAS RN	Risk score	Extractable	CAS RN	Risk score
Squalene	110–02–4	0	Tetradecanoic acid, 2-hydroxyethyl ester	22122–18–5	12
1-Dodecene	112–41–4	4	3-(p-Hydroxyphenyl)-lactic acid	23508–35–2	12
1,3-(1,1-Dimethylethyl)-benzene	1014–60–4	4	1-Oxo-undecanoic acid, ethyl ester	36651–38–4	12
Octadecanoic axcid, tetradecyl ester	17661–50–6	4	4-Hexyloxyphenyl-4′-hexyloxybenzoate	38454–31–8	12
Eicosanoic acid, ethyl ester	18281–05–5	4	Urea	57–13–6	12
4-Tetradecane	54322–28–0	4	2-Hexen-1-ol	2305–21–7	12
Octadecanoic acid, dodecyl ester	5303–25–3	7	Carbonic acid, dipentyl ester	2050–94–4	12
Octadecanamide	124–26–5	7	1-[4-(1-Methylethylphenyl]ethanone	645–13–6	12
1-Octyldecyl ether	6297–03–6	8	Methylenebutanedioic acid, dimethyl ester	617–52–7	12
Acetone	67–64–1	8	4-(1,1,3,3-tetramethylbutyl)-phenol	140–66–9	12
4-tert-Amyl phenol	80–46–6	8	2-(2-(2-Hydroxyethoxy)ethoxy)-acetic acid, methyl ester	86520–57–2	12
1,2,4-Trimethylbenzene	95–63–6	8	13-Hexyloxacyclotri-dec-10-ene-2-one	127062–51–5	12
Butanoic acid, butyl ester	109–21–7	8	3-Ethyl-4-nonanol	19780–72–4	12
Octadecenoic acid, ethyl ester	111–62–6	8	9-Hexadecenoic acid	10030–73–6	12
Octadecanol	112–92–5	8	3-Dodecanol	10203–30–2	12
11-Eicosenoic acid, methyl ester	3946–08–5	8	2-Hydroxyhexanoic acid	6064–63–7	12
13(Z)-Docosenenitrile	73170–89–5	8	1,7-Dihydroxyoctamethyltetrasiloxane	3081–07–0	12
Octadecanoic acid, methyl ester	112–62–9	10	1,11-Undecanedioic acid	1852–04–6	12
Octadecadienoic acid, methyl ester	112–63–0	10	Nonanedioic acid, methyl ester	2104–19–0	12
Octadecanoic acid, hexadecyl ester	1190–63–2	10	Diisooctyl maleate	1330–76–3	12
5-Hydroxy-octadecanoic acid, 8-lactone	1227–51–6	10	2-Hydroxyheptanoic acid	636–69–1	12
7-Oxohydroabietic acid	18684–55–4	10	Hexadecanoic acid, ethyl ester	628–97–7	12
1,4-Benzenedicarboxylic acid, 4-hydroxybutyl-2-hydroxyethyl ester	854985–22–1	11	2-Butanedioic acid, 1,4-bis(2-hydroxypropyl) ester	10095–17–7	12
1-Butanol	71–36–3	11	2-Butanone	78–93–3	12
Propionic acid	79–09–4	11	2-Hydroxypropanoic acid	79–33–4	12
Heptanoic acid	111–14–8	11	Pentanedioic acid	110–94–1	12
2-(1-Butoxy) ethanol	111–76–2	11	2-(2-Ethoxyethoxy) ethyl acetate	112–15–2	12
Ricinoleic acid	141–22–0	11	4-Hydroxy-3-methoxybenzoic acid	121–34–6	12
1,6-Hexanediol	629–11–8	11	Nonanoic acid, ethyl ester	123–29–5	12
Propionic acid	79–09–4	11	Propanoic acid, butyl ester	590–01–2	12
Methyl-1,4-benzenecarboxylic acid	5156–01–4	11	Cyclohexaneacetic acid	5292–21–7	12
2-Butanedioic acid, 1,4-bis(2-hydroxypropyl) ester	10095–17–7	12	2-Heptenoic acid	18999–28–5	12
2,4,6-Trimethyl-1,3,5-cyclohexanetricarboxylic acid	54120–00–2	12	Nonanoic acid, butyl ester	50623–57–9	12
1,1-Diethoxyononane	54815–13–3	12	Hexadcanoic acid, methyl ester	112–39–0	13
Trans-1,2-cyclopentanedicarboxylic acid, dimethyl ester	941–75–3	12	Lauryl acrylate	2156–97–0	13
3-Methyl-2,4-octadienoic acid, methyl ester	91057–12–4	12	1-Hexadecanol	36653–82–4	13
5-Hydroxy-2-methyl-3-hexenoic acid, methyl ester	123061–22–3	12	Octadecenoic acid, methyl ester	112–62–9	13
1-Cyclohexyl-2-ethanone	823–76–7	12	10-Oxo-hexanoic acid, methyl ester	628–97–7	13
1,1-Diethoxyoctane	54889–48–4	12	10-Oxo-octadecanoic acid, methyl ester	870–10–0	13

DISCUSSION

This effort addresses the situation where one is faced with a material that could be used in a package, device or manufacturing system and asks "what is the likelihood that this material contains a certain extractable that could become a leachable in a drug product at high enough levels to produce an adverse safety issue?" Extractables that have been classified as lowest risk would be unlikely to be both present in such a material at levels that could impact safety if the extractables were to become leachables and if they were present would be unlikely to leach in impactful quantities. Extractables classified as highest risk would be more likely to be present in such a material at levels that could impact safety as leachables and, if

they were present, would be likely to leach in impactful levels. Thus, this effort considers the likelihood that the extractables would be present in the material at high enough levels to be potentially meaningful as leachables and the ability of the extractable to be leached into aqueous drug products if it is present in the material.

In general, risk evaluation matrices are based on mathematical models which are more or less empirical. Although these models can be intuitively compelling, it is rare that the models can be fully and quantitatively justified. Thus while all the parameters of the Risk Evaluation Matrix have been explained, they cannot all be quantitatively justified. For example, one cannot offer a quantitative justification for questions such as "why should a solubility of 10 mg/L be assigned a score of 3 (as opposed to 5)]?" except to note that such an assignment seems reasonable and appropriate in the context of the Matrix. Ultimately the value in the analysis of specific extractables via the Matrix is not so much in the absolute magnitude of the calculated TRS but rather in the categorization of the extractable into one of the four risk categories, especially if the extractable is categorized as either lowest risk or highest risk.

As is the case with any ranking system that produces a quantitative outcome, it is pertinent to consider the "resolving power" of the analysis. For example, application of the Matrix to two structurally similar extractables, 9,10-dihydroxy-12,13-epoxy stearic acid and 3-(2,3-Dihydroxyoctyl)-2-oxiraneoctanoic acid (Table VI) produce TRS values of 38 and 35 respectively. This difference in TRS value, arising from the differing amounts of these two substances in their source materials (the first extractable was considered to be a major impurity while the second was considered as a minor impurity) is the difference between the first extractable being placed in the highest risk category and the second extractable being placed in the intermediate risk category. Although one understands the reason why these two extractables have their respective scores and categorizations, one wonders whether the numerical difference in the scores translates into a meaningful difference in the safety risk associated with the two extractables. In this regard, it is clear that the significance of small differences in TRS between individual extractables in terms of safety risk is marginal and is concluded that a difference of 2 units or less in the Total Risk Score is most likely a meaningless difference.

Listing of extractables that were classified as either lowest or highest risk (Tables IX and X) indicate that the risk matrix classification has identified more extractables to be lower risk (approximately 15% of the extractables population) and fewer extractables to be highest risk (approximately 3% of the extractables population), consistent with the observations that (1) extractables tend to be present in their source materials in lower quantities, (2) extractables tend to be associated with specific material types and not with all materials generally, and (3) extractables tend to have low safety scores. Specifically, the extractables in the lowest risk category generally are poorly soluble, are present in only certain materials in low quantities, and have low toxic potential based on Risk Indices, Cramer classification and the lack of mutagencity alerts. Alternatively, extractables in the highest risk category generally have a high solubility and are present in either a specific material type as ingredients or across material groups as high level impurities. These extractables tend to be Cramer Class 3, have mutagencity alerts (or no mutagencity data which is treated as an alert), and have lower Risk Indices (typically 5 mg/day or less). It is noteworthy that three of the ten highest risk compounds are epoxidized acids associated with epoxidized oils that are commonly used as secondary plasticizers and stabilizers. This finding suggests that although such oils may be appropriate for use with polymers used in pharmaceutical applications, one should be sure to account for this type of extractable in any extractables or leachables studies performed on such polymers.

As noted previously, the extractables considered in this manuscript were classified based on their toxicological data with Group 1 extractables being those substances with sufficient and credible toxicological data and Group 2 and 3 extractables being those extractables whose toxicological assessment was based on surrogate compounds. Although there are no readily discernible differences in the distributions as a function of extractables Group, Group 1 extractables are more frequently encountered in the higher risk categories. This outcome is to be expected as it is reasonable to suppose that those extractables with sufficient toxicity data for evaluation (Group 1) would be those extractables that are most commonly encountered and that are present in the materials at higher levels.

Although the process of calculating the Total Risk Scores is generally data-driven and decision-based, the Risk Evaluation Matrix is somewhat empirical. Much of the input information for the matrix (toxicological information, solubilities) is "hard" data as opposed to "soft" intuition- or experience-based claims. Several availability inputs, such as total pool and frequency of occurrence, are experience-based and in the case of this manuscript reflect the experience of one company gained from many years of testing polymeric materials used in diverse medical applications (pharmaceutical containers for parenteral products and drug administration devices). As this experience does not comprehensively cover all medical applications of polymers, it is possible that the availability inputs used in this manuscript are not universally applicable to all medical uses of polymers and that the Total Risk Scores and categorization established in this manuscript are more properly limited to a consideration of parenteral packaging systems and drug administration devices.

Lastly, the Risk Evaluation Matrix was applied to a large population of extractables regardless of the extractable's

source polymer, producing a categorization that was "blind" with respect to the source polymer. One could envision a situation where source polymer would be a means of further segregating the population of extractables. Application of the Risk Evaluation Matrix to each individual group of such a segregated population of extractables could produce a categorization of extractables for each individual polymer that considers only those extractables that are relevant to that polymer. For example, rather than the generic categorization provided in this manuscript, one could produce individual categorizations for individual polymers. Such a segregation of the data population was not performed as source polymer data was not routinely available for the extractables considered in this document.

CONCLUSION

A Safety Evaluation Matrix has been developed, explained and used to categorize a population of extractables. The utility of such a classification lies in its capacity to facilitate the selection of appropriate polymers for use in pharmaceutical systems, to guide the development of analytical methods for extractables discovery, identification and quantitation and to establish which leachables to target in migration studies. Ultimately the categorization establishes a group of lower and higher risk extractables. Thus potential materials of construction can be screened in terms of whether they could contain higher risk extractables, with the understanding that in general it would be desirable for candidate materials to avoid such high risk extractables. For example, as noted previously, three of the ten higher risk extractables were epoxidized acids that are linked to epoxidized oils in polymers. Thus a "first pass" evaluation criterion for materials for potential use in pharmaceutical applications is "does the candidate material contain epoxidized oils?" Although an answer of "yes" might not necessarily mean that the material is unsuited for pharmaceutical applications, such an answer might alert the packaging development team to a potential concern.

Furthermore, the categorization of the extractables could facilitate the development and justification of analytical screening methods used to characterize extracts for extractables. It is well-known that analytical methods used to screen extracts for extractables are not universal and thus that certain extractables elude detection by the methods. If one were to intentionally design an analytical method to produce as much potentially meaningful extractables data as possible, then surely it is the case that greater emphasis would be placed on the method's ability to detect higher risk extractables.

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