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RESEARCH

A Compilation of Safety Impact Information for Extractables Associated with Materials Used in Pharmaceutical Packaging, Delivery, Administration, and Manufacturing Systems

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ABSTRACT: Demonstrating suitability for intended use is necessary to register packaging, delivery/administration, or manufacturing systems for pharmaceutical products. During their use, such systems may interact with the pharmaceutical product, potentially adding extraneous entities to those products. These extraneous entities, termed *leachables,* have the potential to affect the product's performance and/or safety. To establish the potential safety impact, drug products and their packaging, delivery, or manufacturing systems are tested for leachables or extractables, respectively. This generally involves testing a sample (either the extract or the drug product) by a means that produces a test method response and then correlating the test method response with the identity and concentration of the entity causing the response. Oftentimes, analytical tests produce responses that cannot readily establish the associated entity's identity. Entities associated with un-interpretable responses are termed *unknowns.* Scientifically justifiable thresholds are used to establish those individual unknowns that represent an acceptable patient safety risk and thus which do not require further identification and, conversely, those unknowns whose potential safety impact require that they be identified. Such thresholds are typically based on the statistical analysis of datasets containing toxicological information for more or less relevant compounds.

This article documents toxicological information for over 540 extractables identified in laboratory testing of polymeric materials used in pharmaceutical applications. Relevant toxicological endpoints, such as NOELs (no observed effects), NOAELs (no adverse effects), TD_{LO}s (lowest published toxic dose), and others were collated for these extractables or their structurally similar surrogates and were systematically assessed to produce a risk index, which represents a daily intake value for life-long intravenous administration. This systematic approach uses four uncertainty factors, each assigned a factor of 10, which consider the quality and relevance of the data, differences in route of administration, non-human species to human extrapolations, and inter-individual variation among humans. In addition to the risk index values, all extractables and most of their surrogates were classified for structural safety alerts using Cramer rules and for mutagenicity alerts using an in silico approach (Benigni/Bossa rule base for mutagenicity via Toxtree). Lastly, in vitro mutagenicity data (Ames *Salmonella typimurium* and Mouse Lymphoma tests) were collected from available databases (Chemical Carcinogenesis Research Information and Carcinogenic Potency Database).

The frequency distributions of the resulting data were established; in general risk index values were normally distributed around a band ranging from 5 to 20 mg/day. The risk index associated with 95% level of the cumulative distribution plot was approximately 0.1 mg/day. Thirteen extractables in the dataset had individual risk index values less than 0.1 mg/day, although four of these had additional risk indices, based on multiple different toxicological endpoints, above 0.1 mg/day. Additionally, approximately 50% of the extractables were classified in Cramer Class 1 (low risk of toxicity) and approximately 35% were in Cramer Class 3 (no basis to assume safety). Lastly, roughly 20% of the extractables triggered either an in vitro or in silico alert for mutagenicity. When Cramer classifications and the mutagenicity alerts were compared to the risk indices, extractables with safety alerts generally had lower risk index values, although the differences in the risk index data distributions, extractables with or without alerts, were small and subtle.

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KEYWORDS: Extractables, Leachables, Safety assessment, Thresholds, Risk index (RI), Toxicological risk assessment.

LAY ABSTRACT: Leachables from packaging systems, manufacturing systems, or delivery devices can accumulate in drug products and potentially affect the drug product. Although drug products can be analyzed for leachables (and material extracts can be analyzed for extractables), not all leachables or extractables can be fully identified. Safety thresholds can be used to establish whether the unidentified substances can be deemed to be safe or whether additional analytical efforts need to be made to secure the identities. These thresholds are typically based on the statistical analysis of datasets containing toxicological information for more or less relevant compounds.

This article contains safety data for over 500 extractables that were identified in laboratory characterizations of polymers used in pharmaceutical applications. The safety data consists of structural toxicity classifications of the extractables as well as calculated risk indices, where the risk indices were obtained by subjecting toxicological safety data, such as NOELs (no observed effects), NOAELs (no adverse effects), TD_{LO}s (lowest published toxic dose), and others to a systematic evaluation process using appropriate uncertainty factors. Thus the risk index values represent daily exposures for the lifetime intravenous administration of drugs. The frequency distributions of the risk indices and Cramer classifications were examined. The risk index values were normally distributed around a range of 5 to 20 mg/day, and the risk index associated with the 95% level of the cumulative frequency plot was 0.1 mg/day. Approximately 50% of the extractables were in Cramer Class 1 (low risk of toxicity) and approximately 35% were in Cramer Class 3 (high risk of toxicity). Approximately 20% of the extractables produced an in vitro or in silico mutagenicity alert. In general, the distribution of risk index values was not strongly correlated with the either extractables' Cramer classification or by mutagenicity alerts. However, extractables with either in vitro or in silico alerts were somewhat more likely to have low risk index values.

Introduction

Packaging, delivery, administration, and manufacturing systems used with pharmaceutical products may be constructed from plastic materials. Such systems are demonstrated to be suited for their intended use by establishing their ability to

- protect the pharmaceutical product (such as a drug product or solution) that is either stored in the packaging system, delivered, or administered through or via the medical device, or manufactured with a manufacturing system,
- be compatible with the pharmaceutical product,
- be safe when used with the pharmaceutical product, and
- function properly when used with the pharmaceutical product under the relevant clinical conditions.

Demonstrating suitability for intended use is a prerequisite for the registration of a pharmaceutical product and/or its packaging, delivery/administration, or manufacturing systems.

Chemical entities present in these systems can migrate (or leach) into the drug product during that time during which the drug product and these systems are in contact. These extraneous system-derived entities have the potential to affect product performance and/or safety. Experimentally assessing the extent of migration can be accomplished by characterizing the systems for extractable substances (establishing the potential effect) or the packaged drug product for system-related leachables (establishing the actual effect). In either circumstance, the analytical process is the same and typically involves testing a sample (either the extract or the drug product) by a means that produces a response and then correlating the response with the identity and concentration of the entity causing the response. With this information (identity and concentration), the potential safety risk associated with individual extractables (or leachables) can be assessed.

It is often the case that analytical test methods can produce responses more readily than those responses can be used to establish the associated entity's identity and concentration. In the case that an entity's identity cannot be established, the entity is labeled as an unknown and the unknown cannot be toxicologically assessed to directly establish its safety. Nevertheless, it is reasonable to hypothesize

TABLE I
Compiled Information for the Group 1 Extractables

Compound	CAS Registry No.	Toxicological Information					Toxicological Uncertainty Factors (UFs)				Risk Index (RI), mg/day	Cramer Class	Carcinogenicity Alerts		
		Value, mg/kg	Type	Route	Model	Ref.	T1, Inter-species	T2, Intra-species	T3, Route	T4, Type			In Silico[e]		In Vitro[d]
													A	B	
2,4-Dichlorobenzoic acid	50-84-0	830	LD_{50}	oral	mouse	4	10	10	10	10	5.81	3	Neg	Neg	Neg1
Glycerine	56-81-5	4250	LD_{50}	i.v.	mouse	5	10	10	1	10	298	1	Neg	Neg	Neg1[a]
Palmitic Acid	57-10-3	57	LD_{50}	i.v.	mouse	6	10	10	1	10	3.99	1	Neg	Neg	Neg1
Stearic acid	57-11-4	21.5	LD_{50}	i.v.	rats	7	10	10	1	10	1.51	1	Neg	Neg	Neg1
Urea	57-13-6	3000	LD_{LO}	i.v.	dog	8	10	10	1	10	210	1	Neg	Neg	Pos1[a]
Propylene glycol	57-55-6	4200	LD_{LO}	i.v.	rabbit	9	10	10	1	10	294	1	Neg	Neg	Neg1[a]
Linoleic acid	60-33-3	280	LD_{50}	i.p.	mouse	10	10	10	10	10	1.96	1	Neg	Neg	Neg2
Formic acid	64-18-6	2.57	PDE	i.v.	human	11	10	1	1	1	18.0	1	Neg	Neg	Neg1
Acetic acid	64-19-7	45.7	PDE	i.v.	human	11	10	1	1	1	320	1	Neg	Neg	Neg1
Benzoic acid	65-85-0	500	LD_{LO}	oral	human	12	10	1	10	10	35.0	1	Neg	Neg	Neg1[a]
		1700	LD_{50}	i.v.	rats	12	10	10	1	10	119				
		4.4	EPA RfD	oral	human	13	10	1	10	1	3.08				
Hexanal	66-25-1	4890	LD_{50}	oral	rats	14	10	10	10	10	34.2	1	Pos[e]	Neg	N/A
Isopropanol	67-63-0	1024	LD_{LO}	i.v.	dog	15	10	10	1	10	71.9	1	Neg	Neg	Neg1[b]
Acetone	67-64-1	3	PDE	N/A	human	11	10	1	1	1	21.0	1	Neg	Neg	Neg1
Dimethylformamide	68-12-2	470	LD_{50}	i.v.	dog	16	10	10	1	10	32.9	3	Neg	Neg	Neg2[b]
p-Toluenesulfonamide	70-55-3	250	LD_{50}	i.p.	mouse	17	10	10	10	10	1.75	3	Neg	Neg	N/A
		50	NOEL	oral	rats	18	10	10	10	1	3.50				
1-Butanol	71-36-3	310	LD_{50}	i.v.	rats	19	10	10	1	10	21.7	1	Neg	Neg	Neg1
1-Pentanol	71-41-0	15	LD_{LO}	i.v.	cats	20	10	10	1	10	1.05	1	Neg	Neg	N/A
4-Chlorobenzoic acid	74-11-3	1000	LD_{50}	i.p.	rats	21	10	10	10	10	7.00	3	Neg	Pos[f]	Neg1
Ethyl aldehyde	75-07-0	10.6	TD_{LO}	i.v.	human	22	10	1	1	10	7.42	1	Pos[e]	Neg	Neg1[c]
Carbon disulfide	75-15-0	7.6	TD_{LO}	i.p.	rats	23	10	10	10	10	0.053	3	Neg	Neg	N/A
2,2-Dimethylpropanoic acid	75-98-9	900	LD_{50}	oral	rats	24	10	10	10	10	6.30	1	Neg	Neg	N/A
Tributyl acetylcitrate	77-90-7	4000	LD_{50}	i.p.	mouse	25	10	10	10	10	28.0	1	Neg	Pos[g]	Neg2
Diethoxydimethylsilane	78-62-6	9280	LD_{50}	oral	rats	26	10	10	10	10	65.0	3	Neg	Neg	Neg2
2-Butanone	78-93-3	361	TD_{LO}	i.p.	rats	27	10	10	10	10	2.53	1	Neg	Neg	Neg2
Propionic acid	79-09-4	625	LD_{50}	i.v.	mouse	28	10	10	1	10	43.8	1	Neg	Neg	Neg1
Hydroxyacetic acid	79-14-1	1000	LD_{50}	i.v.	cat	29	10	10	1	10	70.0	1	Neg	Neg	Pos1
2-Hydroxypropanoic acid	79-33-4	3194	LD_{50}	i.p.	mouse	30	10	10	10	10	22.4	1	Neg	Neg	N/A

[a]No genotoxocity indicated based on studies in rats, obtained from the Carcinogenic Potency Database (CPDB, 287).
[b]No genotoxicity indicated based on studies in rats and mice, obtained from CPDB (287).
[c]TD_{50} = 153 mg/kg/day in rats, 565 mg/kg/day in hamster.
[d]From CCRIS database (287). Neg1 = negative Ames Salmonella typimurium test. Neg2 = negative Ames and Mouse Lymphoma tests. Pos1 = positive Ames or Mouse Lymphoma test. Pos2 = positive Ames and Mouse Lymphoma test. N/A = No test data available for that compound.
[e]From Toxtree (3, 285) using Benigni/Biossa rulebase. A = considering genotoxic effects, B = considering non-genotoxic effects.
[e]QSA11 rule triggered, simple aldehyde.
[f]QSA31a rule triggered, halogenated benzene.
[g]QSA41 rule triggered, substituted n-alkylcarboxylic acids.

that "scientifically justifiable thresholds based on the best available data and industry practices can be developed for the reporting and safety qualification of leachables . . . and the reporting of extractables from . . . container/closure systems" (1). These scientifically justifiable thresholds would establish those amounts of individual leachables and extractables that could be viewed as representing an acceptable patient safety risk regardless of their actual identity and toxicology

Hypothesis and Purpose

Over the years, a significant quantity of extractables and leachables data, especially their identities, has been published in the chemical literature. For many extractables and leachables, relevant toxicological

TABLE I
(continued)

Compound	CAS Registry No.	Toxicological Information					Toxicological Uncertainty Factors (UFs)				Risk Index (RI), mg/day	Cramer Class	Carcinogenicity Alerts		
		Value, mg/kg	Type	Route	Model	Ref.	T1, Inter-species	T2, Intra-species	T3, Route	T4, Type			In Silico[i]		In Vitro[h]
													A	B	
1,1,2,2-Tetrachloroethane	79-34-5	50	LD_{LO}	i.v.	dog	31	10	10	1	10	3.50	3	Pos[j]	Neg	Pos1[c]
Bisphenol A	80-05-7	5	NOEL	oral	mouse	32	10	10	10	1	0.35	3	Neg	Neg	Neg1
4-tert-Amylphenol	80-46-6	1830	LD_{50}	oral	rats	33	10	10	10	10	12.8	1	Neg	Neg	Neg1
Methacrylic acid, methyl ester	80-62-6	945	LD_{50}	i.p.	mouse	34	10	10	10	10	6.62	1	Neg	Neg	Pos1[b]
		113	LD_{LO}	i.v.	dog	35	10	10	1	10	7.91				
Diethyl phthalate	84-66-2	100	LD_{50}	i.v.	rabbit	36	10	10	1	10	7.00	1	Neg	Pos[l]	Neg1
Diisobutyl phthalate	84-69-5	3990	LD_{50}	i.p.	mouse	37	10	10	10	10	27.9	1	Neg	Pos[l]	Neg1
Dibutyl phthalate	84-74-2	720	LD_{50}	i.v.	mouse	38	10	10	1	10	50.4	1	Neg	Pos[l]	Neg1
Phthalic anhydride	85-44-9	100	LD_{50}	i.p.	guinea pig	39	10	10	10	10	0.700	3	Neg	Neg	Pos1[b]
Benzyl butyl phthalate	85-68-7	159	NOAEL	oral	rats	40	10	10	10	1	11.1	1	Neg	Pos[l]	Neg1[d]
2-Furancarboxylic acid	88-14-2	100	LD_{50}	i.p.	mouse	41	10	10	10	10	0.700	3	Neg	Neg	Neg1
o-Toluenesulfonamide	88-19-7	4870	LD_{50}	oral	rats	42	10	10	10	10	34.1	3	Neg	Neg	Neg1[e]
3,5-Di-tert-butyl-4-hydroxybenzyl alcohol	88-26-6	7000	LD_{LO}	oral	rats	43	10	10	10	10	49.0	2	Neg	Neg	N/A[a]
		175	TD_{LO}	oral	rats	43	10	10	10	10	1.23				
Phthalic acid	88-99-3	250	LD_{50}	i.p.	mouse	44	10	10	10	10	1.75	1	Neg	Pos[l]	Neg1
		102	TD_{LO}	oral	rats	44	10	10	10	10	0.714				
o-Hydroxybiphenyl	90-43-7	100	NOAEL	oral	rats	45	10	10	10	1	7.00	3	Neg	Pos[k]	Pos2[f]
α-Phenylbenzenemethanol	91-01-0	5000	LD_{50}	oral	rats	46	10	10	10	10	35.0	3	Neg	Neg	N/A
Hexanoic acid, 2-ethyl-, diester with triethylene glycol	94-28-0	13677	LD_{50}	dermal	rabbit	47	10	10	10	10	95.7	1	Neg	Pos[m]	N/A
2-Ethyl-1,3-hexanediol	94-96-2	131	LD_{50}	i.v.	rats	48	10	10	1	10	9.17	1	Neg	Pos[m]	Neg2
Benzothiazole	95-16-9	95	LD_{50}	i.v.	mouse	49	10	10	1	10	6.65	3	Neg	Neg	Neg1
o-Xylene	95-47-6	1500	LD_{LO}	i.p.	mammal	50	10	10	10	10	10.5	1	Neg	Neg	Neg1
1,2,4-Trimethylbenzene	95-63-6	1752	LD_{LO}	i.p.	rat	51	10	10	10	10	12.3	1	Neg	Neg	Neg1[g]

[a]No genotoxocity indicated based on studies in rats, obtained from the CPDB (287).
[b]No genotoxicity indicated based on studies in rats and mice, obtained from the CPDB (287).
[c]TD_{50} = 38.3 mg/kg/day in mice.
[d]TD_{50} = 1040 mg/kg/day in rats, no effect reported in mice.
[e]TD_{50} = 3960 mg/kg/day in rats.
[f]TD_{50} = 232 mg/kg/day in rats, no effect reported in mice.
[g]TD_{50} = 4350 mg/kg/day in rats.
[h]From CCRIS database (287). Neg1 = negative Ames Salmonella typimurium test. Neg2 = negative Ames and Mouse Lymphoma tests. Pos1 = positive Ames or Mouse Lymphoma test. Pos2 = positive Ames and Mouse Lymphoma test. N/A = No test data available for that compound.
[i]From Toxtree (3, 286) using Benigni/Biossa rulebase. A = considering genotoxic effects, B = considering non-genotoxic effects.
[j]QSA8 rule triggered, Aliphatic halogens.
[k]QSA47 rule triggered, o-phenyl phenol.
[l]QSA42 rule triggered, phthalate diesters and monoesters.
[m]QSA41 rule triggered, substituted n-alkyl carboxylic acid.

safety information is also available from the literature. Such a database of toxicological safety information may be relevant to published safety thresholds, such as the safety concern threshold (SCT) and qualification threshold (QT). These scientifically justifiable thresholds establish those amounts of individual leachables and extractables that could be viewed as representing an acceptable patient safety risk regardless of their actual identity and toxicology.

This article documents a large number of largely organic, chemically diverse extractables that have been discovered in extraction studies performed on representative materials that could be used in pharmaceutical applications. Toxicological data have been collected for these extractables, and the toxicological data have been subjected to a systematic process of extrapolating the data to the case of long-term, parenterally administered drug products in humans. The extrap-

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