Evaluation of the Potential Extractables from a Chubby Gorilla E-liquid Bottle

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Abstract

Leachable materials in product packaging present a possible hazard to consumers. Toxic materials may migrate out of the packaging into the e-liquid product and be inhaled by the consumer during use of the product. The classical approach to evaluating the potential of packaging material chemicals to migrate into the product is first to perform an extraction study using model solvent systems, and if materials are found at levels of toxicological concern, then a leachables study is performed throughout the shelf life of the product to confirm if the packaging material has the potential to migrate into the product during intended storage and use. The Product Quality Research Institute ("PQRI") Leachables and Extractables Working Group's recommended approach was followed to evaluate a Chubby Gorilla® e-liquid bottle. Specifically, the bottle and cap were tested using the USP 1663 method (Assessment of Extractables Associated with Pharmaceutical Packaging/Deliver Systems). Samples were extracted with aqueous solutions at pH 5.2 and 9.5 and a 50/50% solution of isopropanol and deionized water. The solutions were analyzed by GC/MS (volatiles and semi-volatiles), LC/MS (non-volatiles) and ICP/MS (metals). The bottle and cap did not appear to have the potential to leach materials of toxicological concern above the Safety Concern Threshold (SCT) or Toxicological Threshold of Concern (TTC). Under the conditions of use, the bottle was deemed acceptable as a packaging container for e-liquids.

Introduction

The final PMTA rule requires applicants to submit toxicological information about potential leachables from the container closure system. Chubby Gorilla is a major manufacturer of e-liquid bottles, and their bottles are common in the e-liquid industry. The traditional approach is to first determine if chemicals of toxicological potential can be extracted from the packaging using worst case model systems. These include aqueous and alcoholic systems of varying pH. If chemicals of concern are detected, further studies are conducted using actual e-liquids over the storage life of the product to determine if the extracted chemicals actually leach into the product.

Methods

60 ml clear PET Unicorn bottles with natural child resistant caps were tested (**Figure 1)**. USP 1663, Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems, was followed. Extraction conditions and analyses conducted are shown in **Table 1**.

Table 1. Test Conditions

Solvent	Type of Extraction	Analysis Conducted	Test Article
pH 5.2	Immersion at 50°C, 72 hours.	Volatile Organic Residues GC/MS	Triplicate Samples
		Semi-Volatile Organic Residues GC/MS	
		Non-Volatile Organic Residues (Targeted LC/MS/MS for common additives & TOF w/structural elucidation by accurate mass)	
		Leachable Metals ICP/MS and ICP/OES	
pH 9.5	Immersion at 50°C, 72 hours.	Volatile Organic Residues GC/MS	Triplicate Samples
		Semi-Volatile Organic Residues GC/MS	
		Non-Volatile Organic Residues (Targeted LC/MS/MS for common additives & TOF w/structural elucidation by accurate mass)	
		Leachable Metals ICP/MS and ICP/OES	
50/50 2-Propanol /Water Extraction	Immersion at 50°C, 72 hours	Gross Total Extractables (% w/w)	Triplicate Samples
		Semi-Volatile Organic Residues GC/MS	
		Non-Volatile Organic Residues (Targeted LC/MS/MS for common additives & TOF w/structural elucidation by accurate mass)	

Figure 1. Chubby Gorilla 60 ml Clear Bottle with Natural Cap

Results

Table 2 shows the number of compounds detected under the various extraction conditions and analytical techniques.

Table 2. Number of Compounds Detected Using Various Techniques

Extraction Conditions	Analytical Method	Number of Compounds Detected
pH 5.2	GC/MS Semi-Volatiles	None Detected
pH 9.5	GC/MS Semi-Volatiles	None Detected
50/50 Isopropanol/Water	GC/MS Semi-Volatiles	9
pH 5.2	GC/MS Volatiles	1
pH 9.5	GC/MS Volatiles	1
pH 5.2	LC/MS Non-Volatiles	8
pH 9.5	LC/MS Non-Volatiles	8
50/50 Isopropanol/Water	LC/MS Non-Volatiles	12
pH 5.2	LC/MS Non-Volatiles TOF MS Scan	18
pH 9.5	LC/MS Non-Volatiles TOF MS Scan	16
50/50 Isopropanol/Water	LC/MS Non-Volatiles TOF MS Scan	46
pH 5.2	Metal Analysis	4
pH 9.5	Metal Analysis	6

A total of 70 unique chemicals were identified ranging from 0.01 to 56 µg/bottle (**Table 3**). Many of the same chemicals were identified using the different extraction conditions and analytical techniques. Eight metals were identified (**Table 4).**

Table 3. Unique Chemicals Extracted from the Bottle and Cap

Chemical	Maximum Extracted (µg/bottle)	Chemical	Maximum Extracted (µg/bottle)
(2-dodecylphenyl)methanesulfonic Acid	6.3	Ethylene Terephthalate Cyclic Trimer	1.0
(2S)-1-Hydroxy-3-(stearoyloxy)-2-propanyl(4Z,7Z,10Z,13Z,16Z,19Z)-4,7,10,13,16,19-docosahexaenoate	2.9	Heptanoic Acid	0.23
(2S,3S)-3-Amino-1,2-heptadecanediol	53	Hexadecane	0.93
{5-[(2-Biphenylyloxy)sulfonyl]-2-thienyl}acetic acid	1.7	Hexadecanoic Acid	22
10-Hendecenoic Acid	0.29	Irgafos 168	1.3
13-Docosenamide, (Z)-	1.7	Irganox 1010	1.35
1-Hydroxy-3-[(3-hydroxydecanoyl)oxy]-2-propanyl (9Z)-9-hexadecenoate	1.3	Irganox 1076	0.74
2-(Bis{2-[2-(hexyloxy)ethoxy]ethyl}amino)ethanol	3.2	Laurixamine	2.8
2,4-Di-tert-butylphenol	2.9	Lauryldiethanolamine	56
2-[2-(Decylamino)ethoxy]ethanol	12	Methyl (1a'S,1b'S,5'S,5a'S,6a'S)-5'-(alpha-Lallopyranosyloxy)-4-(4-hydroxy-3-methoxybenzoyl)-5-oxo-1a',5',5a',6a'-tetrahydro-1b'H,5H-s[orp[furan-2,6'-oxireno[3,4]cyclopenta[1,2-c]pyran]-2'-carboxylate	1.5
2-[2-(Octadecylamino)ethoxy]ethanol	5.3	Methyl {2-[2-(3,4-dihydroxyphenyl)-3,5-dihydroxy-4,8-dioxo-9,10-dihydro-4H,8H-pyrano[2,3-f]chromen-10-yl]-6-methoxyphenoxy}acetate	1.2
2-[2-(Octylamino)ethoxy]ethanol	8.5	N,N-Dimethyloleamide	2.0
2-[Dodecyl(2-hydroxyethyl)amino]ethyl stearate	4.3	N-nonylnonanamide	1.1
2-[2-[2-(Dodecylamino)ethoxy]ethoxy}ethanol	27	Nonanoic Acid	0.63
2-[2-[2-(Octylamino)ethoxy]ethoxy}ethanol	5.8	Nonylphenol Ethoxylates	4.4
2-[2-[4-(Dimethylamino)-2-(dodecyloxy)butoxy]ethoxy}ethanol	3.5	n-Propyl acetate	0.071
3-(Hexadecylamino)-1,2-propanediol	27	Octadecanoic Acid	2.3
3,6,9-Trioxa-12-azatetracosan-1-ol	9.1	Octanoic Acid	1.9
3-Butyl-6,9,12-trioxa-3-azahexadecan-1-ol	2.1	Oleamide	14
4-(Dodecyloxy)benzenesulfinic Acid	5.1	Oleic Acid	5.4
4-[2,7-Bis(3-carboxypropyl)-6-hydroxy-3-oxo-3Hxanthen-9-yl]isophthalic acid	6.2	Oxidized Irgafos 168	2.6
4-Decylbenzenesulfonic Acid	1.1	Palmitamide	<1.0
9-Octadecenamide, (Z)-	4.7	Palmitamidohexadecanediol	1.2
Compound Similar to 2-[2-Decylamino)ethoxy]ethanol	25	PEG-3 Capramine	11
Compound Similar to 2-[2-[2-Dodecylamino)ethoxy]ethoxy}ethanol	2.0	PEG-3 Myristamine	5.3
Cyclic and Linear Siloxanes with a Dimethyl siloxane(-(CH3)2SiO-) Repeat Unit	7.4	PEG-3 Oleamine	4.7
Decanal	1.1	PEG-3 Palmitamine	4.9
Decanoic Acid	2.2	Possible Ionic Surfactant	1.9
Dibutyl phthalate	1.8	Possible Slip-Agent	3.3
Dimethyldibenzylidene sorbitol	3.7	Tetradecanoic Acid	2.0
Dioctylamine	1.1	Triethylsilanol	0.085
Dodecane	1.8	Trimethyl 3-hydroxy-6-(2-hydroxy-5-methylbenzoyl)-1,2,4-benzenetricarboxylate	3.1
Dodecanoic Acid	1.3	Ultranox 626 Diphosphate	1.2
Erucamide	6.1	Ultranox 626 Monophosphate	1.3
Ethyl 2-palmitoylhydrazinecarboxylate	1.1	Undecylbenzenesulfonic Acid	3.6

Table 4. Maximum Amount of Metals Extracted Exceeding Background

Metal	Maximum Extracted (µg/bottle)
Antimony	0.39
Barium	0.39
Calcium	1.5
Copper	0.03
Manganese	0.017
Molybdenum	0.27
Potassium	280
Tin	7.9

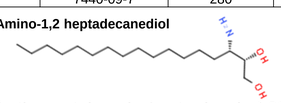
The Product Quality Research Institute (PQRI) Leachables and Extractables Working Group's recommended evaluation approach was followed. A Safety Concern Threshold (SCT) was used to determine if any identified extracted chemicals require further evaluation. The FDA threshold of regulation for substances used in food-contact packaging of 1.5 µg/day was utilized as the SCT. The SCT was converted into a relative amount, expressed in terms of the amount of an individual extractable in the product in the bottle. The amount of E-liquid consumed per day was used to determine the relative Safety Concern Threshold (rSCT). Using the SCT of 1.5 µg/day and the daily consumption of 2.58 ml yields a relative SCT of 0.581 µg/ml. Since the bottle contains 60 ml, the rSCT was calculated as **34.86 µg/bottle**. Only 2 chemicals and a metal exceeded the rSCT (Highlighted). If an extractable exceeded the rSCT, the Toxicological Threshold of Concern (TTC) was determined for the extracted chemical based on its Cramer Classification. Inhalation TTC's (Tluczkiewicz et al. 2016) were used for the analysis: 2 µg/day and 4.26 mg/day for Cramer Class III and I compounds, respectively. Any Cramer Class II chemicals were presumed to be Class III for this safety evaluation process

Table 5 lists the chemicals that exceeded the rSCT, their Cramer Class, and the respective inhalation TTC. Lauryl diethanolamine was detected but it did not exceed its TTC of 108 µg/bottle. (2S,3S)-3-Amino-1,2 heptadecanediol was also detected. The amount, 53 µg/bottle exceeds the TTC of 0.05 µg/bottle for a Cramer Class II chemical. The compound does not have a chemical abstract service number and is only identified by its ChemSpider ID. It is not on the TSCA inventory and is not on any list of carcinogens, mutagens, or reproductive toxicants. **Figure 3** shows the structure of (2S,3S)-3-Amino-1,2 heptadecanediol. There is no toxicity information available on the chemical. The chemical is not predicted to be a mutagen or carcinogen by the CAESAR QSAR modeling software. Based on the levels, the structure, and QSAR modeling results it is unlikely that (2S,3S)-3-Amino-1,2 heptadecanediol presents a significant leachable hazard.

Table 5. Extractable Compounds that Exceeded the Relative Safety Concern Threshold and their TTCs

Tentatively Identified Compound	CAS Number or ChemSpider ID	Average (µg/bottle)	Cramer Class	Inhalation TTC (µg/bottle)
Lauryl diethanolamine	1541-67-9	56	I	108
(2S,3S)-3-Amino-1,2 heptadecanediol	8261006	53	II	0.05
Potassium	7440-09-7	280	-	-

Figure 3. Structure of (2S,3S)-3-Amino-1,2 heptadecanediol



Potassium was identified in the metal analysis at a level of 280 µg/bottle. Potassium is an ion that is required for life. It occurs naturally in foods. The Dietary Reference Intake for females 19 years and older is 2,600 mg/day and for males 19 years and older 3,400 mg/day (National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Food and Nutrition Board; Committee to Review the Dietary Reference Intakes for Sodium and Potassium 2019). The potential amount of potassium in the product as a result of potential migration from the packaging (280 µg/day) will not result in significant exposure when compared to the normal daily recommended consumption. Potential potassium migration from the plastic bottle and cap does not present a risk to the consumer.

Conclusion

An extractable study was performed on the 60ml Chubby Gorilla bottle. The bottle and cap do not appear to have the potential to leach materials at levels of toxicological concern. The container closure system is appropriate for use with e-liquids.

References

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