

## Technical Report No. 55

Detection and Mitigation of  
2,4,6-Tribromoanisole and  
2,4,6-Trichloroanisole Taints and  
Odors in the Pharmaceutical and  
Consumer Healthcare Industries

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# **PDA Task Force on Detection and Mitigation of 2,4,6-Tribromoanisole and 2,4,6-Trichloroanisole Taints and Odors in the Pharmaceutical and Consumer Healthcare Industries**

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The content and views expressed in this Technical Report are the result of a consensus achieved by the authorizing Task Force and are not necessarily views of the organizations they represent.

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## EXECUTIVE SUMMARY

Since December 2009, there have been multiple recalls of pharmaceutical and over the counter drug products by at least five companies for musty, moldy odor caused by trace levels of 2,4,6-Tribromoanisole (TBA) taints. Based on literature review, a bench marking survey and data made available to the PDA Task Force it was concluded that the taint was caused by trace contamination of High Density Polyethylene packaging containers with highly volatile and odorous TBA during transportation and storage on wood pallets constructed in Puerto Rico from 2,4,6-Tribromophenol (TBP)-treated lumber from South America. The moisture content of the wood was sufficient to promote fungal growth resulting in the biomethylation of the halophenol to its haloanisole.

The trace concentrations found in customer complaint samples, i.e., ppb-ppt levels, require matrix-specific sampling, pre-concentration, and gas chromatography-mass spectrometry/olfactory detection that is only suitable for analytical confirmation of taints and not routine monitoring.

Possible risk mitigation steps identified by the Task Force include not constructing pallets from TBP treated lumber, controlling the moisture content of wood to levels not conducive to fungal growth, improved supply chain awareness of haloanisole taints, other sources of halophenols and adequate environmental control and ventilation in warehouses and during transportation.

Toxicological and safety studies conducted on TBA demonstrated no mutagenicity or systemic toxicology in rodents when dosed for up to 28 days at levels a billion-fold higher than potential human exposure from the recalled product. TBA dosing produced no diarrhea or any macroscopic or microscopic pathological effects along the GI tract in rat toxicity studies. Although nausea was reported by consumers sensing the musty, moldy odor, adverse event analysis by multiple recalling companies have not established a causal relationship between TBA and gastrointestinal events. Therefore, reactions of disgust to TBA taints appears to be sensory and/or behavioral and not toxicological and therefore is not a safety risk.

Based on the high margin of safety demonstrated in toxicity studies, there is no meaningful analytical threshold that can be based on toxicity. It is therefore necessary for individual companies to consider how the odor is being perceived by their customers and the likelihood that perception to the odor could impact patient therapy, i.e. the concern is that the musty, moldy odor from these taints could increase the likelihood that patients will not take their medication.

# Table of Contents

<b>1.0 INTRODUCTION</b> .....	<b>1</b>	6.4 Laboratory Controls .....	29
1.1 Scope and Purpose.....	1	6.5 Environmental Monitoring .....	34
1.2 Overview of the Uses of Halophenols 2,4,6-Tribromophenol (TBP) and 2,4,6-Trichlorophenol (TCP) in Industry.....	1	6.6 Sensory Panel Examination of Material for Off-Odors .....	35
1.3 Fungal Biomethylation of 2,4,6-Tribromophenol (TBP) and 2,4,6-Trichlorophenol (TCP) To Generate 2,4,6-Tribromoanisole (TBA) and 2,4,6-Trichloroanisole (TCA) .....	2	6.7 Moisture Content of Wood .....	37
1.4 Sensory and Physiochemical Properties of 2,4,6-Tribromophenol (TBP), 2,4,6-Trichlorophenol (TCP), 2,4,6-Tribromoanisole (TBA), 2,4,6-Trichloroanisole (TCA), and Related Compounds .....	4	<b>7.0 PRODUCT QUALITY COMPLAINTS, ADVERSE EVENTS, NOTIFICATION TO REGULATORY AGENCY, AND RECALL PROCEDURES</b> .....	<b>39</b>
1.5 Migration and Diffusion of 2,4,6-Tribromophenol (TBP), 2,4,6-Trichlorophenol (TCP), 2,4,6-Tribromoanisole (TBA), and 2,4,6-Trichloroanisole (TCA) .....	6	7.1 Product Quality Complaints .....	39
1.6 Quality and Risk Management.....	6	7.1.1 TBA Signal Identification and Verification (Complaint Data).....	40
<b>2.0 GLOSSARY OF TERMS</b> .....	<b>7</b>	7.1.2 Complaint Investigation .....	40
<b>3.0 PRINCIPLES AND TOOLS</b> .....	<b>13</b>	7.1.3 Root Cause Analysis .....	40
3.1 The Supply Chain.....	13	7.2 Adverse Events (AEs) .....	41
3.2 Good Distribution Practices (GDPs) .....	14	7.3 Notification to Regulatory Agency .....	41
3.3 Quality Risk Management .....	14	7.4 Recalls.....	41
<b>4.0 INDUSTRY BENCHMARKING</b> .....	<b>15</b>	<b>8.0 TOXICOLOGY AND SAFETY</b> .....	<b>42</b>
4.1 Industry Examples of Encounters in Supply Chain That Resulted in Product Tainting .....	15	8.1 Introduction and Background.....	42
4.2 TBA and TCA Taint Examples from Food and Beverage Industries.....	15	8.2 Literature Review on TBA.....	42
4.3 TBA and TCA Taint Examples from Pharmaceutical and Consumer Healthcare Industries .....	17	8.3 Specificity of Haloanisoles and Halophenols .....	43
4.4 PDA TBA Industry Benchmarking Survey .....	20	8.3.1 TCP .....	43
<b>5.0 DISTRIBUTION FLOW</b> .....	<b>21</b>	8.3.2 TBP .....	44
5.1 Pallets .....	22	8.4 Data Generated on TBA .....	45
5.2 Shipping Containers .....	24	8.4.1 Non-Clinical (Toxicology) .....	45
5.3 Corrugate .....	25	8.4.2 Bacterial Reverse Mutation Assay (Ames). 45	
5.4 Plastics .....	26	8.4.3 Single-Dose Oral Rat Study.....	45
<b>6.0 ANALYTICAL</b> .....	<b>27</b>	8.4.4 5-Day Repeat-Dose Oral Rat Study .....	46
6.1 Overview .....	27	8.4.5 28-Day Repeat-Dose Oral Rat Study .....	46
6.2 Method Review .....	27	8.4.6 TBA Exposure in Rats .....	46
6.3 Method Acceptance Criteria (for Haloanisole and Halophenol Concentrations).....	28	8.5 Discussion.....	47
		8.5.1 TBA Theoretical Thresholds.....	47
		8.6 Results/Conclusions .....	49
		<b>9.0 QUALITY RISK MANAGEMENT</b> .....	<b>50</b>
		9.1 Risk Assessment.....	51
		9.1.1 Risk Identification .....	51
		9.1.2 Risk Analysis .....	53
		9.1.3 Risk Evaluation .....	53
		9.2 Risk Control.....	53
		9.2.1 Risk Reduction.....	53
		9.2.1.1 In Pallet.....	54
		9.2.1.2 In Warehouse .....	54
		9.2.1.3 In Shipping .....	54
		9.2.1.4 In Customer Complaints .....	54
		9.2.2 Risk Acceptance.....	54

9.3 Risk Review.....	55	11.4.1 Pallet Manufacturers.....	66
<b>10.0 CONCLUSION .....</b>	<b>56</b>	11.4.2 Shipping/Transportation.....	67
<b>11.0 APPENDIX.....</b>	<b>58</b>	11.4.3 Storage, Warehousing, Distribution .....	68
11.1 Supplemental Pallet and Shipping Container Information .....	58	11.4.4 Pharmaceutical and Consumer Healthcare Manufacturing .....	68
11.1.1 Best Practices .....	58	11.5 Sample SOP on Pallet Control Procedures..	68
11.1.2 Transport and Distribution.....	60	11.6 Shipping Container Flow Chart.....	72
11.1.3 Storage throughout the Supply Chain ...	61	<b>12.0 ACRONYMS.....</b>	<b>73</b>
11.1.4 Pharmaceutical and Consumer Healthcare Manufacturers .....	61	12.1 Regulatory Authorities .....	73
11.2 Pallet Suppliers and Oversight of Suppliers	62	12.2 Technical Groups .....	73
11.3 Auditing/ Risk Assessment of Wood Pallets and Shipping Containers .....	64	12.3 Technical Terms .....	73
11.4 Supply Chain Quality Risk Management ...	65	<b>13.0 ADDITIONAL READING MATERIAL .....</b>	<b>74</b>
		<b>14.0 REFERENCES.....</b>	<b>76</b>

## FIGURES AND TABLES INDEX

<b>Figure 1.3-1</b> Halophenol to Haloanisole Biomethylation Conversions .....	2	<b>Table 1.3-2</b> "Parts per" Notations.....	29
<b>Table 1.3-1</b> Representative Reports in the Literature on the Biomethylation of Halophenols .....	3	<b>Figure 6.4-1</b> Example Mass Spectra for TCA and TBA .....	31
<b>Table 1.3-2</b> Equilibrium Moisture Content of Wood at Different Temperatures and Humidity Related to Fungal Growth .....	4	<b>Table 6.4-1</b> Reference Standard Limit of Detection by Method.....	33
<b>Table 1.4-1</b> Sensory Characteristics of Selected Organohalogenes .....	5	<b>Table 6.4-2</b> Approximate Sample Limit of Detection by Matrix Type by Method Type .....	33
<b>Table 1.4-2</b> Physicochemical Attributes of Organohalogenes of Interest.....	5	<b>Table 6.4-3</b> Typical Sample Preparation Approaches by Matrix .....	34
<b>Figure 3.1-1</b> The Pharmaceutical and Consumer Healthcare Supply Chain.....	13	<b>Table 8.3.1-1</b> TCP and TCA Exposure Levels .....	44
<b>Table 4.1-1</b> Representative Literature References to Organohalogen Taints in the Food, Beverage, Consumer Healthcare, Pharmaceutical Industries .....	15	<b>Table 8.5-1</b> TBA versus Theoretical Threshold Levels .....	48
<b>Table 4.2-1</b> Concentration of Organohalogenes in Beer and Packaging Materials .....	16	<b>Figure 9.0-1</b> Quality Risk Management Process for Haloanisole Taints.....	50
<b>Table 4.3-1</b> Examples of TBA and TCA Taint Cases from Pharmaceutical and Consumer Healthcare Industries.....	18	<b>Table 9.1.1-1</b> Risk Identification .....	51
<b>Table 6.3-1</b> Concentration-Dependent Pharmaceutical Guidances .....	29	<b>Table 11.4.1-1</b> Quality Risk Management for Pallet Manufacturers .....	66
		<b>Table 11.4.2-1</b> Quality Risk Management for Shipping/Transportation.....	67
		<b>Table 11.4.3-1</b> Quality Risk Management for Storage, Warehousing, Distribution .....	68
		<b>Table 11.4.4-1</b> Additional Risks to Manufacturers .....	68
		<b>Figure 11.6-1</b> Shipping Container Flow Chart .....	72

# 1.0 Introduction

## 1.1 Scope and Purpose

The scope of this technical report covers 2,4,6-tribromoanisole (TBA) and 2,4,6-trichloroanisole (TCA) taints and odors. These particular musty, moldy taints have very low thresholds of detection, at parts per trillion (ppt), and high volatility relative to other organohalogen taints. Taints arise from an external source as opposed to off-odors or off-flavors from internal changes to a product (i.e., microbial spoilage).

The purpose of this report is to provide guidance on how to detect and mitigate TBA and TCA odors and taints. Well recognized in the food and beverage industries (1–4), the literature features knowledge from these industries regarding the origin of these odors and taints, analytical methods developed, and risk management strategies employed. In 2009, this became an issue for the pharmaceutical and consumer healthcare industries with product recalls from four companies due to the risk of product exposure to the TBA taint from tribromophenol-treated wood pallets. Recalls from additional firms continued through 2011.

This report will provide background on issues with TBA and TCA taints, highlighting:

- Uses of 2,4,6-tribromophenol (TBP) and 2,4,6-trichlorophenol (TCP) in industry
- Role of fungal halophenol methylation that generates TBA and TCA haloanisole taints
- Sensory and physiochemical properties of TBP, TCP, TBA and TCA
- Case examples from food and beverage industries with root causes and remedial actions
- Recent examples of TBA taint recalls from the pharmaceutical and consumer healthcare industries

Additionally, this report will provide guidance on signal detection from adverse event and/or product quality complaints and resulting recalls, toxicology and safety, analytical method development and use, supply chain controls, risk analysis and mitigation. Definitions of technical terms used in this report can be found in the glossary. The principles and tools used to manage these taints are also defined in this report.

## 1.2 Overview of the Uses of Halophenols 2,4,6-Tribromophenol (TBP) and 2,4,6-Trichlorophenol (TCP) in Industry

Multiple examples from the literature of the food and beverage industry indicate that TBP and TCP, precursors to the TBA and TCA taints, can enter the supply chain from various sources and can also form in the environment under certain conditions. Examples of these sources are highlighted below.

TBP is used as a wood preservative in various parts of the world. Although not registered for use in the United States and the European Union, TBP is known to have been used as a wood preservative in Central America, South America, Eastern Europe and Northern Asia, according to the literature (2,3). Additionally, TBP is known to be used as fire-retardant agents in insulation (e.g., walls, ceiling tiles), epoxy resins (e.g., floor sealants), polyurethanes, plastics, paper and textiles (5). TBP has also been used in pesticides, antiseptic agents and detergents (6). It is also known that naturally occurring phenol residues in water and wood materials can be halogenated in the presence of bromine under certain conditions to form TBP (7).

According to the 2005 Concise International Chemical Assessment Document No. 66 (8), TBP is reacted with sodium hydroxide to form the sodium salt of tribromophenol in water, which is used as a wood preservative. Standard application methods of pressure and vacuum impregnation, dipping, brushing, and spraying of the wood are used. The solution is very effective in controlling insects, fungi, and bacte-