

Application Note

Abstract

1,4-Dioxane routinely makes headlines when found in water or consumer products. A potential byproduct of the sulfation process, 1,4-dioxane is generated in the manufacture of alcohol ether sulfates and may be created in the ethoxylation process using ethylene oxide.

Current methodology, including US EPA methods are normally performed on water matrices. The FDA has methods for consumer products and pharmaceuticals in both water-soluble and water-insoluble products.

This application note will compare the detection of 1,4-dioxane in consumer products using the US EPA method, currently in use at numerous testing facilities, to the FDA methods for water-insoluble products. Eleven different consumer products, ranging from soaps to lotions to toothpaste, will be compared by both methods with the Tekmar HT3 headspace autosampler.



Introduction

1,4-Dioxane routinely makes headlines when it is detected in consumer product containing sodium laurel sulfate. The FDA has requested manufacturers of sodium laurel sulfate remove a substantial amount of 1,4-dioxane by vacuum stripping. The methodology typically used to examine 1,4-dioxane in consumer products are US EPA methods for the determination of 1,4-dioxane in water.¹

Two potential issues exist with this water-based methodology. First, not all consumer products are totally soluble in water. Secondly, consumer products are regulated under the Food Drug and Cosmetic acts of the FDA, not the USEPA.

The FDA, through the United States Pharmacopeia (USP), currently has at least 2 different methods for the determination of 1,4-dioxane in their regulated products. The first, the recently updated headspace method, USP <467>², is used for the determination of residual solvents in pharmaceutical products. This GC/FID method has sample preparation procedures for both water-soluble and water-insoluble products. The water-insoluble products use solvents other than water to dissolve the product, allowing better release of low-level impurities from the matrix. The samples are then analyzed by static headspace.

The second method, an In-Process revision to the USP/NF General Chapters <228>³, is used to determine ethylene oxide and 1,4-dioxane by GC/FID in products prepared from ethylene oxide. A weighed portion of the test substance, about 1 g, is placed into a headspace vial, and 1.0 ml of N,N-dimethylacetamide and 0.2 mL of water added. The samples are then analyzed with a static headspace method. The limit of this test for 1,4-dioxane, if found, is not more than 10 µg per gram of sample.

The technique from USEPA Method 522, utilizing selected ion monitoring (SIM) and deuterated dioxane, 1,4-dioxane-d₈, will be used with the Thermo Focus GC/DSQII MS to provide the lowest detection limit. This also allows isolation of 1,4-dioxane from the other components in the potentially complex matrices found in formulated consumer product samples. The samples will be prepared in headspace vials and sampled with the static headspace method of the HT3.

The Universal Gas Law, $PV=nRT$, is critical to headspace analysis. The three variables, temperature (T), pressure (P) and volume (V), directly affect the sensitivity of analytical systems. The volume of solution and the solvent matrix will be evaluated for all samples. The static vial pressure will be documented.

Sample Information

Eleven consumer products ranging from bubble solutions, lotions and soaps were obtained. The products and some of the label compounds which might include 1,4-dioxane, are listed in Table 1.

Product	Label Ingredients	
	First Listed	Other
Bubble Solution	No ingredients listed	
Mouthwash	Water	Poloxamer 407
Body Powder	Zea Mays Starch	
Deodorant	Cyclopentasiloxane	PPG-14 butyl ether, PEG-8 disterate,
Shampoo and Conditioner	Water	Ammonium Laureth Sulfate, Ammonium Lauryl Sulfate, PEG-14M
Shampoo	Water	PEG-80 Sorbitan Laurate, Sodium Trideceth Sulfate, PEG-150 Disterate
Body Wash	Water	PEG-80 Sorbitan Laurate, Sodium Laureth Sulfate, PEG-150 Disterate
Bar Soap	Soap	
Toothpaste	Water	Sodium Lauryl Sulfate
Skin Cream	Water	Steareth-21, Steareth-2
Body Lotion	Water	Polysorbate 20

Table 1: Label Ingredients for Consumer Products Tested for 1,4-Dioxane.
 The other ingredients listed are potential sources for 1,4-dioxane^{4,5,6}.

Experimental-Instrument Conditions

The HT3 Automated Headspace Analyzer was connected to a Thermo Focus GC/DSQ II MS system for this study. A Restek Rtx®-VMS column was used. Table 2 displays the HT3 method parameters, while Table 3 displays the GC/MS full and SIM scan parameters.

Teledyne Tekmar HT3 Parameters			
Variable	Static Value	Variable	Static Value
Constant Heat Time	On	Mixing Time	10.00 min
GC Cycle Time	30.00 min	Mixing Level	Level 5
Valve Oven Temp	140°C	Mixer Stabilize Time	5.00 min
Transfer Line Temp	140°C	Pressurize	15 psig
Standby Flow Rate	50 mL/min	Pressurize Time	2.00 min
Platen/Sample Temp	95°C	Pressurize Equil Time	0.20 min
Platen Temp Equil Time	1.00 min	Loop Fill Pressure	12 psig
Sample Equil Time	45.00 min	Loop Fill Time	2.00 min
Mixer	On	Inject Time	1.00 min

Table 2: HT3 Headspace Conditions

Thermo Focus GC Parameters	
Column	Restek Rtx-VMS, 20m, 0.18mm ID, 1µm df
Oven Program	35 °C for 7 min, 20 °C/min to 200 °C for 0 min, run time - 15.25 min
Inlet:	Temperature - 200 °C, Split Ratio - 20:1 Helium Carrier Gas; Constant Flow - 0.7mL/min; P&T Adapter
Thermo DSQ II Parameters	
Mass Spec	Acquisition Time - 12.50 minutes; Transfer Line and Source Temp – 200 °C
Full Scan	35.0 to 350.0 m/z, Scan Rate - 1492.11
SIM Scan	Masses - 43.0 m/z, 46.0 m/z, 58.0 m/z, 64.0 m/z, 88.0 m/z, 96.0 m/z, Width - 0.50; Dwell Time - 100

Table 3: Thermo Focus GC / DSQ II MS Full and SIM Parameters

Standard Preparation

The 1,4-dioxane-d8 50 ppm internal standard was prepared by diluting 250 µL of a stock 2000 µg/mL standard in 10 mL of P&T methanol. All samples, standards and blanks are spiked with 10 µL of this internal standard solution.

The 1,4-dioxane 2000 g/mL stock standard was prepared by diluting 20µL of reagent grade 1,4-dioxane into 10 mL of P&T methanol. The 50 ppm working standard was prepared by diluting the 250 µL of the stock standard into 10 mL of P&T methanol. The standards and duplicates of the consumer products are spiked with 10 µL of this 50 ppm standard.

Standards were prepared, in triplicate, in three matrix solutions for this application. The first solution was 7.5 mL of water containing 1 g of sodium sulfate. The second solution was a mix 2.5 mL of water with 5 mL of DMSO. The third solution was 7.5 mL of DMSO.

The volume portion of the Universal Gas Law equation, $PV=nRT$, is critical for headspace analysis. The headspace volume was kept constant by insuring that the sample volume and the added liquid volume totaled 7.5 mL. The pressure portion is also critical for headspace analysis. The different solvent mixtures were used to assist in determining the static vial pressure (SVP) for the water and the non-water based consumer product solutions.

Sample Preparation

The sample amount used for all of the consumer products was 2.5 g. The consumer products were prepared in duplicate for each solvent condition to allow one sample to be spiked with 10 µL of the 50 ppm 1,4-dioxane standard. These spike recoveries show that if 1,4-dioxane is present, it is not being held in the solution due to the complex chemical matrix of consumer products.

The first solvent condition used 1 g of sodium sulfate along with 5 mL of deionized water. This set of samples was used to compare to the current EPA type of water methods, employed by numerous testing laboratories.

The second solvent condition was the addition of 5 mL of DMSO. This will allow the complex chemical matrix to dissolve similarly to the current FDA methods for non-soluble products for situations where the water may not be the most applicable solvent.

Standards Results

The selected ion monitoring (SIM) data was evaluated using the mass ions of 1,4-dioxane, m/z 88, and 1,4-dioxane- d_8 , m/z 96, for all of the samples, standards, and blanks. The relative standard deviation (%RSD) for the internal standard, the calibration standard, and their response factors (RF) for the three calibration standards, and the internal standards through the entire analysis are compared in Table 4. The static vial pressure (SVP) is also included for the different solvent matrices.

The selected ion chromatograms for 1,4-dioxane, m/z 88, and 1,4-dioxane- d_8 , m/z 96, and the full range scan, m/z 35 to m/z 350, were compared for the three different solvent mixtures. Figure 1 shows this comparison.

Matrix	SVP	% Relative Standard Deviation		
		Std	IS	RF
Calibration Standards (n=3)				
Water	10.1	43.4	43.3	1.3
Mix	7.1	11.2	12.1	4.7
DMSO	3.2	2.2	3.0	1.8
Internal Standards Determined for Standards and Blanks through Sequence				
Water (n=14)	9.9	NA	55.3	NA
Mix (n=7)	7.1	NA	20.9	NA
DMSO (n=13)	3.3	NA	10.8	NA

Table 4: Static Vial Pressure (SVP) and % Relative Standard Deviation for the 1,4-Dioxane Standard Solution in Water, Water:DMSO (1:3), and DMSO. The table includes separate data for the three standards and the internal standard for the sample blanks through the entire analysis sequence.

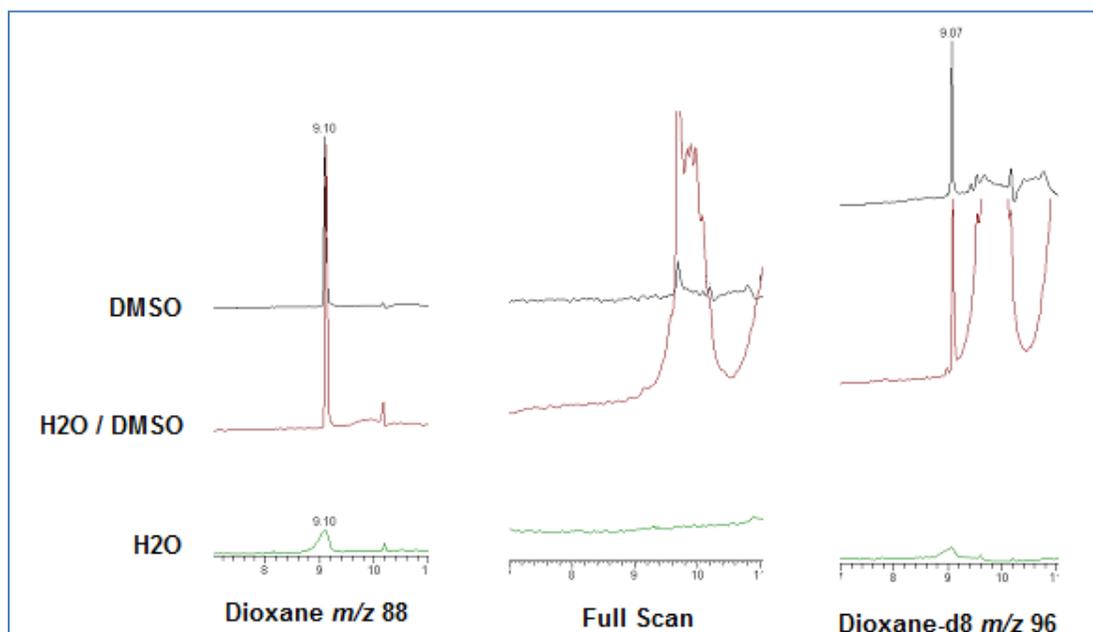


Figure 1: Comparison of the SIM Chromatograms for 1,4-Dioxane (m/z 88, left), the Internal Standard 1,4-Dioxane- d_8 (m/z 96, right) and the same Region by Full Scan. The chromatograms presented are the standards in water (green), in water/DMSO (red) and in DMSO (black).

Sample Results

The evaluation of the samples for 1,4-dioxane was performed in three steps. The first was to tentatively identify 1,4-dioxane in the samples by comparing the retention time of any peak observed in the m/z 88 SIM chromatogram to the retention time of the reference standard. If a peak was observed, then the fragment mass, m/z 58, was evaluated and if present, the ratio to the m/z 88 ion was compared. If this ratio was acceptable, then the concentration, in parts per million (ppm), was calculated based on the weight of the sample.

The concentrations of 1,4-dioxane detected in the samples were calculated for both the water and DMSO solutions. Table 5 summarizes the concentration of 1,4-dioxane for both the water and DMSO sample preparation along with data from Table 1 for the potential source of 1,4-dioxane, if the major ingredient is water and the static vial pressure (SVP) for the samples in water and DMSO.

Product	Source	Water	SVP		1,4-Dioxane (ppm)	
			Water	DMSO	Water	DMSO
Bubble Solution	No	Yes	9.8	7.3	0	0
Mouthwash	Yes	Yes	11.8	7.8	0	0
Body Powder	No	No	10.2	3.5	0	0
Deodorant	Yes	No	7.1	3.6	0	0
Shampoo and Conditioner	Yes	Yes	10.5	6.2	12.4	20.3
Shampoo	Yes	Yes	10.4	6.7	5.6	5.1
Body Wash	Yes	Yes	10.3	6.8	0.16	0.33
Bar Soap	No	No	7.5	3.3	0	0
Toothpaste	Yes	Yes	9.6	4.8	0	0.01
Skin Cream	Yes	Yes	6.8	4.4	0	0.01
Body Lotion	Yes	Yes	9.1	6.0	0.14	0.09

Table 5: Summary Comparing the Data from Table 1 Concerning the Potential Source of 1,4-Dioxane, if the Major Sample Ingredient is Water, the Static Vial Pressure (SVP) for the Different Solvent to the calculated ppm 1,4-Dioxane Detect for the Samples.

The data indicated that some of the samples had different values depending on the solvent matrix. Figure 2 is a photograph of the water and the DMSO sample vials for the shampoo and conditioner sample at approximately 95°C.

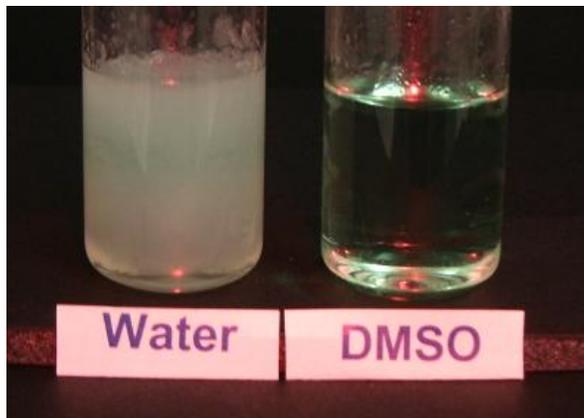


Figure 2: Photograph of the Shampoo and Conditioner Sample in Water (Left) and DMSO (Right) at approximately 95 °C.

The SIM chromatograms of two of the samples, the shampoo and conditioner and toothpaste, for both of the solvents were compared in Figure 3 and 4. The toothpaste sample indicated a possible 1,4-dioxane peak in the water solution, however the corresponding confirmation ion at mass 58 was not observed in the appropriate ratio as the standard.

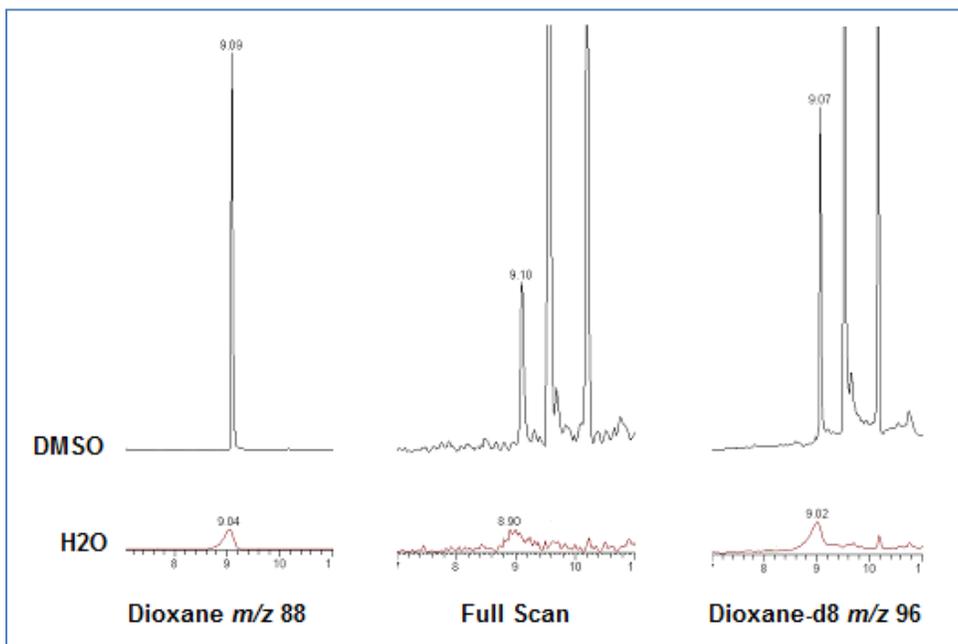


Figure 3 - Comparison of the SIM Chromatograms of the Shampoo and Conditioner Sample for 1,4-Dioxane (m/z 88, left), the Internal Standard 1,4-Dioxane-d8 (m/z 96, right) and the Same Region by Full Scan. The chromatograms presented are the sample in water (red) and in DMSO (black).

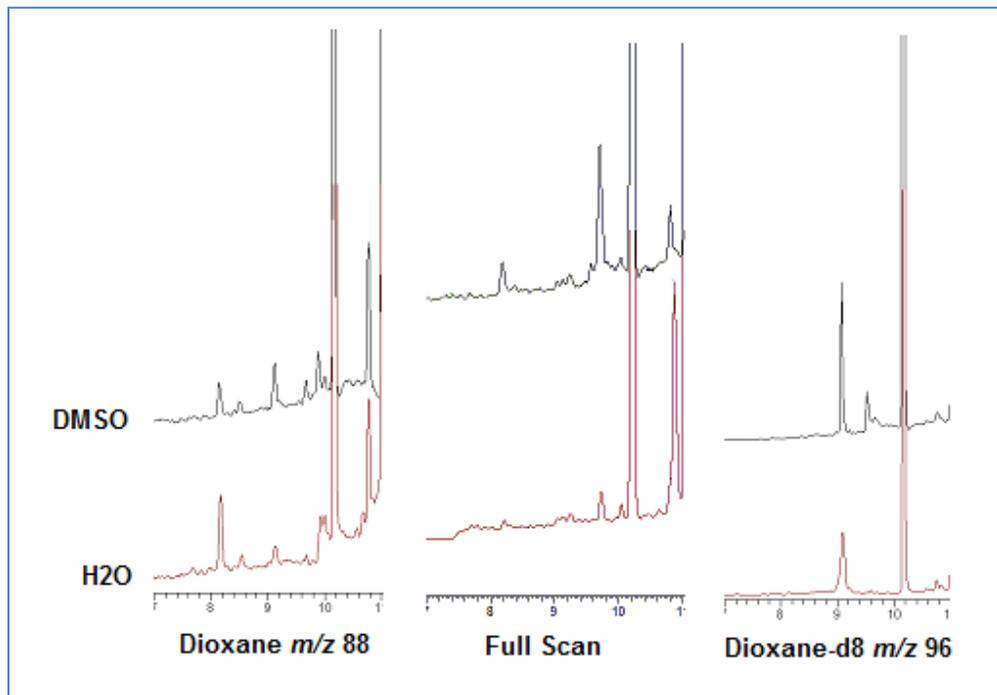


Figure 4 - Comparison of the SIM Chromatograms of the Toothpaste Sample for 1,4-Dioxane (m/z 88, left), the Internal Standard 1,4-Dioxane- d_8 (m/z 96, right) and the same Region by Full Scan. The chromatograms presented are the sample in water (red) and in DMSO (black).

Conclusions

Currently, low levels of 1,4-dioxane, a concern for consumers due to its possible toxicity, are analyzed using a variety of different methods. US EPA methodology, used on water-based matrices, utilizes SIM with a deuterated internal standard to achieve ppb detection limits. The FDA, through the USP, has two methods to detect 1,4-dioxane as a residual solvent, both using GC/FID and solvents other than water to dissolve the samples. These methods were combined in this application note to determine if improvements can be made in their ability to detect 1,4-dioxane.

Consumer products can contain complex mixtures of ingredients, both water-soluble and water-insoluble. When assaying these samples for 1,4-dioxane using heated static headspace methods, sample homogeneity is critical for consistent partitioning of the analytes from the matrix to ensure accurate data.

Eleven consumer products were analyzed for 1,4-dioxane by the US EPA water method and the FDA solvent method. The water method detected 1,4-dioxane in 4 of the 11 samples. The FDA solvent method detected 1,4-dioxane in 6 of the 11 samples. The FDA solvent method detected greater concentrations of 1,4-dioxane for 2 of the 4 samples than the US EPA method.

This application note demonstrates that the headspace analysis of 1,4-dioxane can be greatly influenced by the matrix used to prepare the sample. Better data is obtained when the sample and the solvent create a homogenous solution. The data also indicates that by changing the solvent matrix from water to DMSO, the static vial pressure, one of the critical factors from the Universal Gas Law, can be lowered.

By using solvents with boiling points greater than water, higher vial temperatures may be used, which may partition more 1,4-dioxane into the headspace. This also makes further method development and optimization possible using the HT3's Method Optimization Mode (M.O.M.) to increase recoveries and lower detection limits for 1,4-dioxane in these matrices.

References

1. Results of Testing for 1,4-Dioxane by Gas Chromatography/Mass Spectrometry, www.organicconsumers.org/bodycare/
2. USP 35 – NF 30 (United States Pharmacopeial Convention) General Information Chapter, Residual Solvents <467>, Rockville, MD: USP 2012, pp. 185
3. 35 – NF 30 (United States Pharmacopeial Convention) General Information Chapter, Ethylene Oxide and Dioxane <228>, Rockville, MD: USP 2012, pp.143
4. Fact Sheet, 1,4-Dioxane, Sept 2007, Agency for Toxic Substance and Disease Registry, Division of Toxicology and Environmental Medicine, U.S. Department of Health and Human Services <http://www.astdr.cdc.gov/toxfaq.html>
5. Ethoxylated Compounds, Chemical of the Day, <http://chemicaloftheday.squarespace.com/most-controversial/2011/1/22/ethoxylated-compounds.html>
6. 1,4-Dioxane FAQs, The Campaign for Safe Cosmetics, <http://safecosmetics.org/article.php?id=282>