Considerations for Uncertainty Factor Determination in Medical Device Extractables Analysis

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Plain Language Summary

An important aspect of safety evaluation for medical devices is to perform chemical analysis to understand the identities of chemicals that can be released from devices along with their quantities. This work reviews how to set the minimum levels appropriately in order to capture possible safety concerns.

Abstract

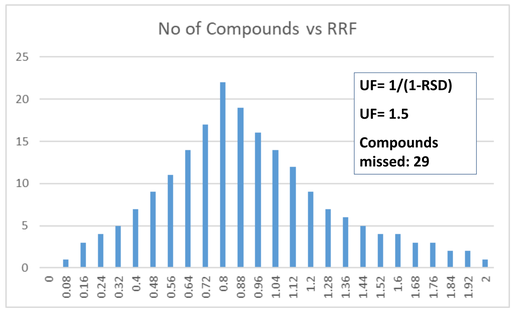
- **The recently released standard ISO 10993-18:2020, which describes chemical characterization approaches, defines the Analytical Evaluation Threshold (AET) as the minimum reporting limit for the chemical analysis.**
- **One of the factors contained in the AET equation is uncertainty factor (UF).**
- **UF is intended to reduce the AET to be inclusive of extractables that respond less than the signal that the AET is based on.**
- **This study explored considerations for curating a response factor database that is used to calculate UF values.**
- **A panel of potential medical device extractable compounds (primarily common polymer additives, a portion which are of toxicological concern) were analyzed with various instruments.**
- **Response factors of compounds were obtained by analyzing surrogate standards and followed by calculation of the limit of quantification to ensure that the UF is inclusive of all compounds in the database.**
- **The goal is to expand the database with more compounds to generate information on the minimum number and minimum structural diversity needed for consideration of UFs.**

Experimental Methods

- **Direct injection or static headspace sampling mode coupled with GC/FID/MS (7890B/5977B Agilent) equipped with an internal splitter for simultaneous FID/MS signal acquisition.**
- **An UHPLC/UV/CAD/MS system (Dionex Ultimate 3000 with Corona Ultra RS with Agilent 6540B UHD QTOF-MS) generated simultaneous or sequential UV, CAD and MS(+) and MS(-) signals.**

Theory and Background

- **Mullis et al described the basis of UF calculation in their 2008 presentation. (Mullis 2008)**
- **This report included how to construct a response factor database to calculate UF .**
  - **The majority of the discussion was based on GC/MS data**
  - **Requirements for internal standard were described as:**
    - ***"Well-behaved" in the particular analytical method***
    - ***Stable in the analytical matrix***
    - ***Compatible with the analytical technique***
    - ***Not interfered ~~with~~ by other analytes or components in the analytical matrix***



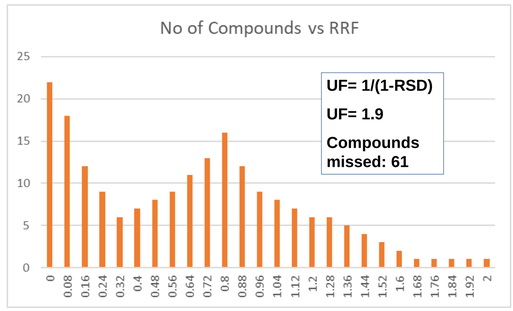


Figure 1: Normal distribution (blue) vs Multi-mode distribution (orange) : Synthetic data based on 200 compounds. Synthetic data based on literature and laboratory data. (Jenke 2012, Jordi 2020) RRF: Relative Response Factor; RSD: Relative Standard Deviation

References:

Jenke, D.; Odufu, A., Journal of Chromatographic Science 2012, 50 (3), 206-212

Jordi, M. A.; Rowland, K.; Liu, W.; Cao, X.; Zong, J.; Ren, Y.; Liang, Z.; Zhou, X.; Louis, M.; Lerner, K., J Pharm Biomed Anal 2020, 186, 113334.

Mullis, J. O.; Granger, A.; Quin, C.; Norwood, D. L., Leachables and Extractables. Smithers Rapra, Dublin, Ireland, , Dublin, Ireland, , 2008.

Summary

- **Synthetic data shows that if the data has multi modal distribution, then a higher number of compounds may be missed by the UF calculation.**
- **The preliminary data indicated that the UF value for HS-GC/FID and HS-GC/MS was 6 to >10**
- **UF values for UHPLC using UV and CAD detectors were less than 3.**
- **The UF calculation for GC/MS and LC/MS yielded undefined values due to high variability of the signal between analytes (high RSD values).**
- **These findings highlight a need for additional work to define an equation for UF that provides useful results.**

Results and Analytical Parameters

		Semi-Volatiles/Volatiles	Volatiles	
Metrics	**Units**	**GC/MS**	**HS-GC/FID**	**HS-GC/MS**
RSD†	(%)	107	94	84
Uncertainty Factor (UF) [U.D. = Undefined]†	(#)	U.D.	>10	6
Number of Analytes	(#)	7	15	14
Total Number of Targeted Analytes in Mixture	(#)	7	15	15
Detection [Criteria: >0.95 linearity]	(%)	100	100	93
Average Degree of Saturation	(#)	8	2	2
Average Molecular Weight	(g/mol)	277	89	93
Column	n/a	DB-5MSUI 30 m x 0.25 mm x 0.25 µm Film	DB-624 60 m x 0.32 mm x 1.4 µm Film	
Injection Volume	(mL)	1.0E-03	1.0E+00	1.0E+00
Empty Volume Per Vial	(mL)	n/a	1.4E+01	1.4E+01
Sample Volume Analyzed	(mL)	1.0E-03	6.0E+00	6.0E+00
Splitter Ratio	Ratio	n/a	1 to 1	1 to 1
Average LOQ [Based on Sample Volume Analyzed]	(ng)	5.9E-02	6.5E+04	6.3E+02

*Does not include DEHP and BPA due to co-eluting internal standard peaks

†Determined without undetected compounds

Table 1:GC/MS and HS-GC-FID/MS Data.

		Non-Volatiles/Semi-Volatiles			
Metrics	**Units**	**LC/MS (+)**	**LC/MS (-)**	**UV (280 nm)***	**CAD (High Filter)***
RSD†	(%)	188	182	39	60
Uncertainty Factor (UF) [U.D. = Undefined]†	(#)	U.D.	U.D.	2	3
Number of Analytes	(#)	8	6	8	5
Total Number of Targeted Analytes in Mixture	(#)	11	11	11	11
Detection [Criteria: >0.95 linearity]	(%)	73	55	73	45
Average Degree of Saturation	(#)	11	11	11	15
Average Molecular Weight	(g/mol)	494	542	473	612
Column	n/a	Agilent 120 Å Poroshell 2.7 µm SB-C18 2.1 mm x 100 mm			
Injection Volume	(mL)	3.0E-03	3.0E-03	3.0E-03	3.0E-03
Empty Volume Per Vial	(mL)	n/a	n/a	n/a	n/a
Sample Volume Analyzed	(mL)	3.0E-03	3.0E-03	3.0E-03	3.0E-03
Splitter Ratio	Ratio	n/a	n/a	n/a	1 to 1
Average LOQ [Based on Sample Volume Analyzed]	(ng)	3.8E-01	1.8E+00	1.0E+00	2.7E+00

*Does not include DEHP and BPA due to co-eluting internal standard peaks

†Determined without undetected compounds

Table 2:LC/UV/CAD/MS Data.