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Risk Assessment of Leachable Substances from a Ventricular Catheter Using Exhaustive Extractions

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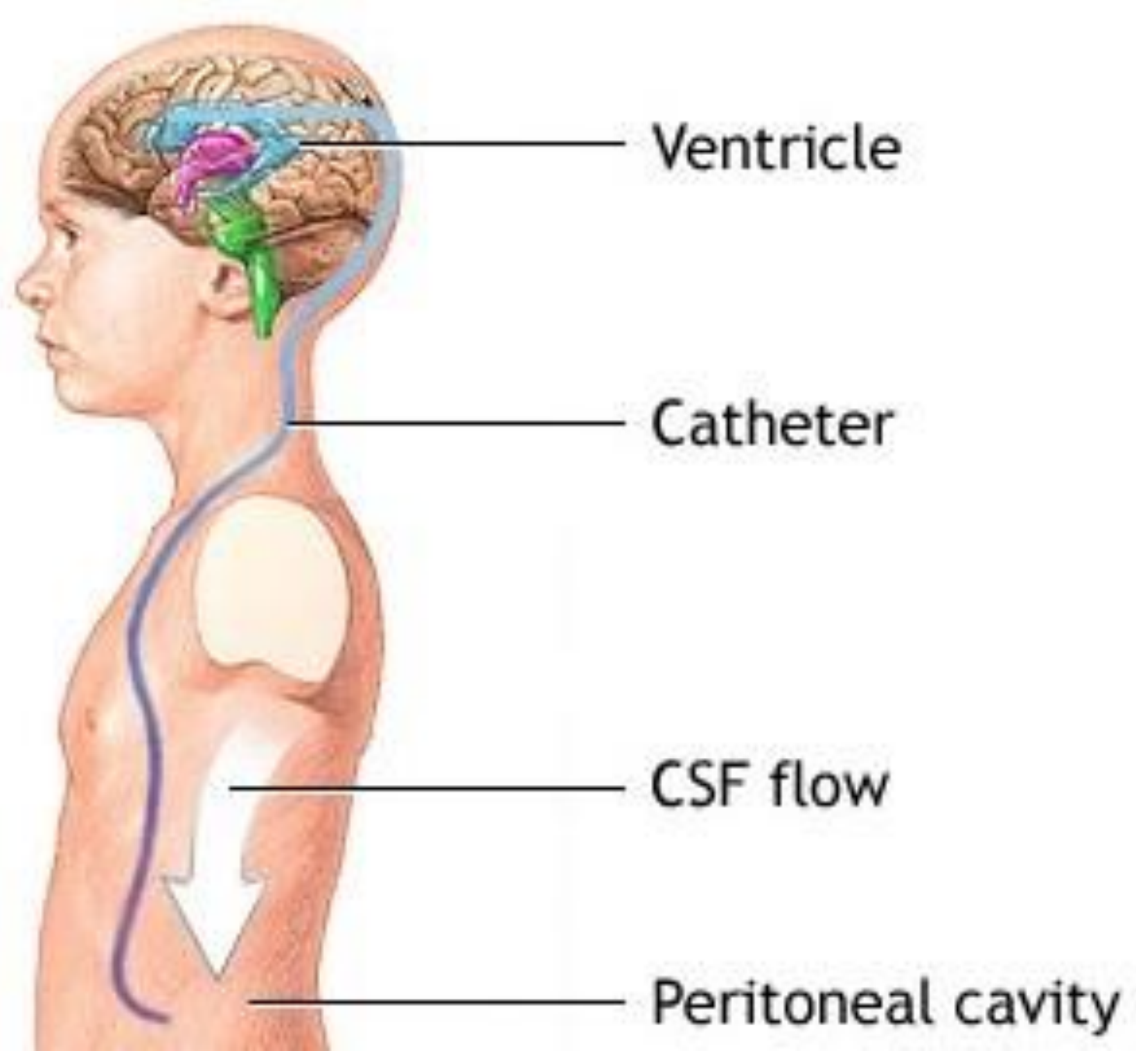
INTRODUCTION

As part of a toxicological risk assessment (TRA), an extractables/leachables (E/L) analysis was conducted for a **ventricular catheter**, a medical device used to drain CNS fluid that is causing excess intracranial fluid pressure. To thoroughly capture leachables that may be released during long term implantation, prolonged extractions were employed using non-volatile residue (NVR) to monitor the endpoint of exhaustive release of organic chemicals. Exhaustive extractions provide essential data for the TRA of permanent implants; however, determining the endpoint of such extractions can be costly and time-consuming. In this study, the cumulative NVR recovered using consecutive 72-hour extractions, with solvent replenishment after each, was higher than the NVR measured after a single, prolonged extraction. To enable the use of prolonged extractions to achieve the goals of an exhaustive extraction, a bias correction was introduced to adjust the analytical data from the prolonged extractions for a more accurate estimate of the total releasable amount of analytes for use in the risk assessment.

VENTRICULAR CATHETER



ANALYTICAL APPROACH

Extractions of the catheter were conducted with polar, nonpolar, and amphipathic solvents, using water, hexane, and isopropanol (IPA) to bracket the range of leaching behaviors possible under different conditions. E/L analysis was conducted following ISO 10993-12, using a surface area-to-solvent ratio of 6 cm^2 per 1 mL solution. All extractions were performed in triplicate.

Preliminary sequential extractions were conducted to determine the duration for a prolonged extraction to capture all of the analyte mass that could be leached from the device. Extractions were conducted for 72-hours at 50˚ C, and followed by solvent removal and analysis for NVR. Fresh extraction solvent was added and a second 72-hour extraction was performed along with another NVR analysis. The process was repeated until extracted NVR had declined to a level <10% of the initial concentration (criteria specified by ISO 10993).

Using new test articles, extractions were performed for a duration indicated by the sum of the preliminary extraction timeframes, and associated extracts were analyzed for volatile organic compounds (VOCs) and semivolatile organic compounds (SVOCs) by GC/MS, non-volatile organic compounds (NVOCs) by LC/MS, and metallic elements by ICP.

NVR DATA: SEQUENTIAL vs. PROLONGED EXTRACTIONS

As shown in Table 1, successive extractions with IPA and hexane reached an exhaustive endpoint (<10% of intial extraction) after three 72-hour extractions at 50˚ C. With purified water, two 72-hour extractions were needed to achieve the exhaustive endpoint.

Table 1: NVR Results from Extractions with Isopropyl Alcohol (IPA)

NVR Based on IPA Extractions with Solvent Replenishment

Extracted NVR, mg	Total mg	0-72 hrs.	72-144 hrs.	144-216 hrs.
Sample 1	68.8	47.3	17.0	4.5
Sample 2	76.3	52.0	19.3	5.0
Sample 3	72.5	50.5	16.6	5.4
NVR Normalized to First Extraction:		**100 %**	**35 %**	**9.9 %**

NVR by Prolonged IPA Extraction

NVR Test No.	0-216 hrs.
Sample 1	59.0
Sample 2	56.5
Sample 3	59.8
NVR Ratio for Sequential vs. Prolonged Extraction	**1.24**

NVR Based on Hexane Extractions with Solvent Replenishment

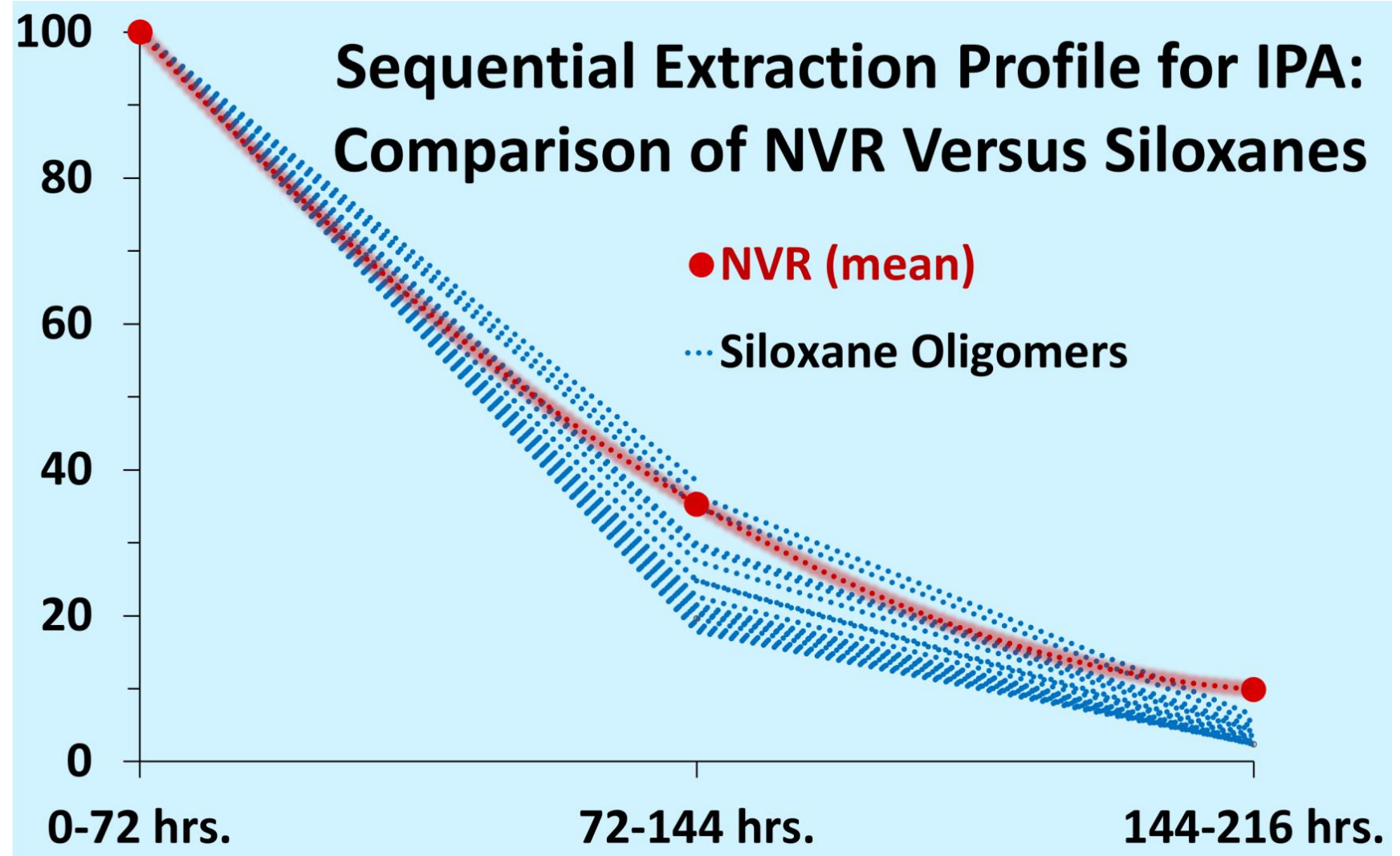
Extracted NVR, mg	Total mg	0-72 hrs.	72-144 hrs.	144-216 hrs.
Sample 1	74.9	48.7	23.2	3.0
Sample 2	70.8	52.0	15.6	3.2
Sample 3	18.1	N/A	14.9	3.2
NVR Normalized to First Extraction:		**100 %**	**36 %**	**6.2 %**

NVR Based on Aqueous Extractions with Solvent Replenishment

Extracted NVR, mg	Total mg	0-72 hrs.	72-144 hrs.
Sample 1	0.1	0.1	0.0
Sample 2	0.1	0.1	0.0
Sample 3	0.1	0.1	0.0
NVR Normalized to First Extraction:		**100 %**	**0 %**

CHEMICAL-SPECIFIC EXTRACTION PROFILES

The extractable NVR measurements from sequential extractions with IPA are plotted against the normalized extraction profiles obtained for individual siloxane oligomers reported from a series of extractions conducted under the same conditions, based on GC/MS analyses performed by another laboratory (data not used in this risk assessment). Reasonable agreement is seen between NVR and siloxane depletion profiles.



CHEMICAL-PHYSICAL PROPERTIES vs. EXTRACTION RATE

Different leaching profiles seen in prolonged (continuous) extractions versus sequential extractions with solvent replenishment can be explained by well-known chemical-physical properties.[1,2,3,4,5,6]

- An equilibrium governs the ratio of the analyte concentration in solution to that within the polymer. Once this ratio is attained, solvent replacement would be needed to facilitate additional leaching.
- Compound solubility can limit the leachate concentrations achieved by extraction. This was not a limiting factor for IPA or hexane extractions as siloxane oligomers are highly miscible in these solvents.
- Solid-phase migration occurs at a diffusion-limited rate. Under some conditions, a slow analyte diffusion rate can impede attainment of solid/liquid equilibrium, extending the total extraction timeframe.
- Polydimethylsiloxane polymers can swell after solvent immersion by more than 50% by weight in hexane solution and >10% with IPA. The entrapped solvent is not removed after one extraction, and contains dissolved analytes that would not be included in the calculation of extracted mass. This may cause an 8-10% bias if 1 mL solvent volume is used per 6 cm^2 of test article, with a thickness of 0.5mm

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SEQUENTIAL vs. PROLONGED EXTRACTION COMPARISON

Statistical Comparison of Means for Successive-Extraction Versus Single-Extraction NVR

The Satterwthwaite t-test is a modified t-test used when 2 samples have unequal variances and sample sizes.

$$t = \frac{\overline{X}_1 - \overline{X}_2}{\sqrt{\frac{s_1^2}{N_1} + \frac{s_2^2}{N_2}}}$$

The degrees of freedom (ν) associated with the variance estimate is approximated by the Welch-Satterthwaite equation:

$$\nu \approx \frac{\left(\frac{s_1^2}{N_1} + \frac{s_2^2}{N_2}\right)^2}{\frac{s_1^4}{N_1^2\nu_1} + \frac{s_2^4}{N_2^2\nu_2}}$$

Where: $\nu_1 = N_1 - 1$, $\nu_2 = N_2 - 1$, and the degrees of freedom (d.f.) is equal to the truncated integer of v.

NVR sum of extractions (with solvent replenishment):
Std.Dev.(S_1): 3.750
Mean (X_1): 72.533 mg NVR

NVR for prolonged extraction:
Std.Dev.(S_2): 1.721
Mean (X_2): 58.433 mg NVR

$$\text{t-calculated} = \frac{(X_1) - (X_2)}{((S_1)^2/3 + (S_2)^2/3)^{0.5}} = 5.92$$

$$\nu = \text{Integer of: } \frac{(S_1{}^2/3 + S_2{}^2/3)^2}{S_1{}^4/(3^2\times 2) + S_2{}^4/(3^2\times 2)} = 2$$

Critical value for test statistic = t-(0.05,2 d.f.) = 2.92

The calculated t-statistic exceeds the critical value, so the difference between means is significant at a 5% level ($P < 0.05$).

The significant difference justifies use of an adjustment factor based on the ratio of the sum of NVR to the prolonged NVR.

Adjustment Factor = Mean (X1) / Mean (X2) = 1.24

RISK ASSESSMENT

The risk assessment was performed according to methods described in ISO 10993-17. Analytical results for the prolonged extractions were reported in units of µg/device and were **adjusted upwards by a factor of 1.24** to correct for exhaustive extraction bias.

To estimate a daily exposure in µg/day, the total leachable amount of each analyte was divided by a 365-day exposure period, although the device may remain in use for a much longer period. This conservative estimate of exposure was used for adult, child, and neonate patients. For organic analytes, published toxicity data (e.g., NOAELs) were used to derive Tolerable Exposure (TE) levels, with a Margin of Safety (MOS) calculated for each compound. Estimated daily exposures to metallic analytes were compared to Permissible Daily Exposure (PDE) levels. All substances were below a TE or PDE, indicating adverse effects are not expected from clinical exposure. Actual exposures during clinical use are likely to be lower than these estimates due to the conditions of the chemical analysis; e.g., elevated temperature and use of nonpolar solvents that can swell polymer materials.

Table 2: Potential Exposures to Extractable Organics and Tolerable Exposure (TE) Levels.

Compound	Extraction Solvent	Daily Exposure (µg/day)	Neonate		Child		Adult	
			TE (µg/day)	MOS	TE (µg/day)	MOS	TE (µg/day)	MOS
Acetone	IPA	4.79	700	150	2000	420	14000	2900
	Water	0.0592		12000		34000		>100000
D6 Siloxane	IPA	2.28	140	61	400	180	2800	1200
	Hexane	1.91		73		209		1500
D9 Siloxane	IPA	6.17	140	23	400	65	2800	450
	Hexane	7.57		18		53		370
12 PDMS oligomers	IPA	74.7	140	1.9	400	5.4	2800	37
	Hexane	78.7		1.8		5.1		36

CONCLUSIONS

Using a 2-step approach to conducting exhaustive extractions, the total leachable mass of each substance was able to be accurately estimated using prolonged extraction data in conjunction with NVR analysis of sequential extraction data. By employing the modified study design in the chemical characterization and risk assessment, the Sponsor was able to achieve approval of their ventricular catheter by both FDA and European medical authorities. The analytical approach was cost-effective and avoided having to conduct separate GC/MS and LC/MS analysis of individual extracts for a series of consecutive extractions.