



Monitoring Hazardous Drugs in the United States

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US Wipe Sampling Studies

- McDevitt et al. (1993)-Cyclophosphamide
- Connor et al. (1999)-Cyclophosphamide, Ifosfamide, Fluorouracil
- Connor et al. (2002)-Cyclophosphamide, Ifosfamide, Fluorouracil
- Wick et al. (2003)- Cyclophosphamide, Ifosfamide
- Harrison et al. (2006)-Cyclophosphamide, Fluorouracil
- NIOSH (2008)-Cyclophosphamide, Ifosfamide, Fluorouracil, Doxorubicin, Paclitaxel, Cytarabine

US Wipe Sampling Methodology

- Most studies used methods of Sessink et al. (1992, 1994)
- NIOSH study followed procedure of Larson et al. (2002, 2003)

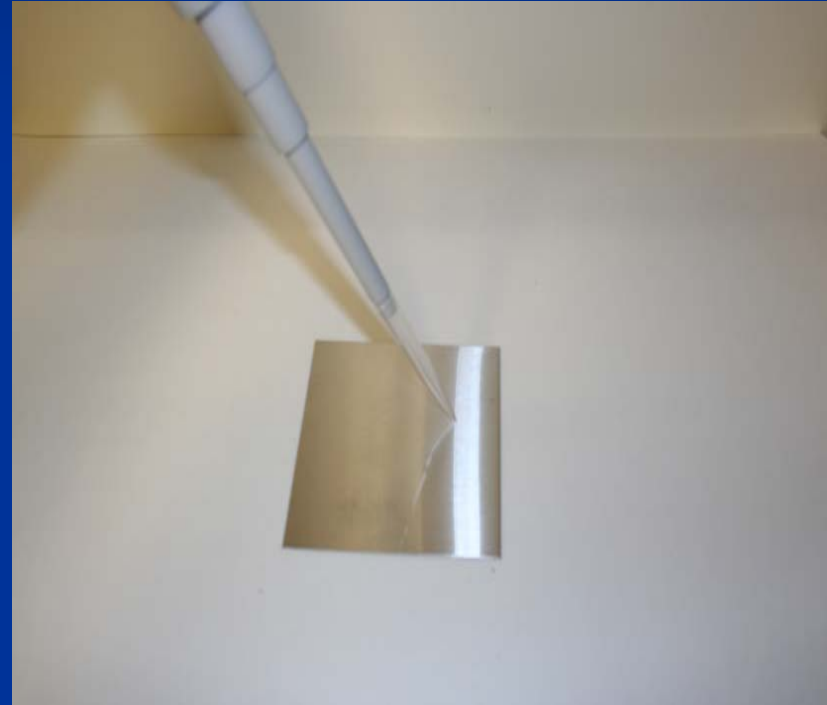
Wipe Sample Recovery Procedure

- Drugs were recovered from three representative surfaces:
 - Stainless steel
 - Formica®
 - Vinyl flooring
- 10 cm X 10 cm



Drug Recovery Procedure

- 5 Concentrations of each drug were applied to 5 replicates of each material
- Drug solutions were allowed to air dry for 2 hours



Drug Recovery Procedure

- 250 μL of solvent (Methanol, 25%; Acetonitrile, 10%; Milli Q water, pH 6.0, 65%) were applied to the material and then wiped with a Whatman 5.5 cm filter paper
- The process was repeated and filters combined



Drug Recovery Procedure

- Both filter wipes were placed in a 125 ml polypropylene, screw-top jar
- 9.5 ml of solvent were added to the jar and it was sonicated for 30 minutes



Drug Recovery Procedure

- The filtrate was removed from the jar with a syringe and filtered through a 0.22 μm filter



Drug Recovery Procedure

- 1.9 mL of sample were added to a polypropylene tube containing 200 μL of internal standard (10 ng/mL hexamethylphosphoramide)



Liquid Chromatography-Mass Spectrometry (LC-MS)

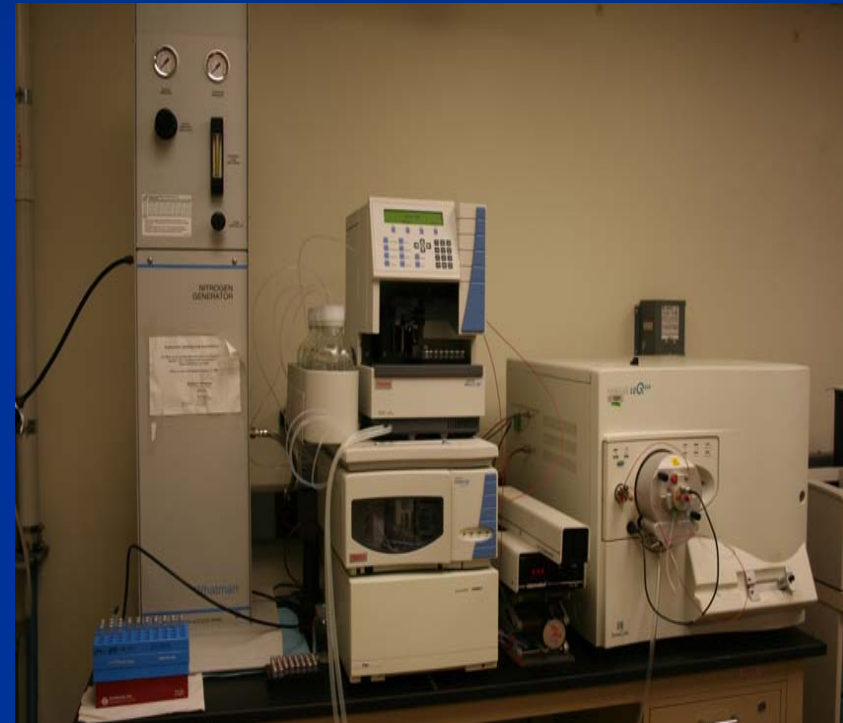
- Sensitive, confirmatory analytical methods needed for accurate quantification of antineoplastic drugs at low levels
- LC-MS increasingly cited in literature as analytical method of choice
- Techniques for generating ions from solution (electrospray, APCI) compatible with polar, ionizable analytes in polar media (most antineoplastic drugs)
- Drug detection limits 0.6 to 2.0 ng/mL with current LC-MS instrument (newer systems designed for higher sensitivity)

Liquid Chromatography-Mass Spectrometry (LC-MS)

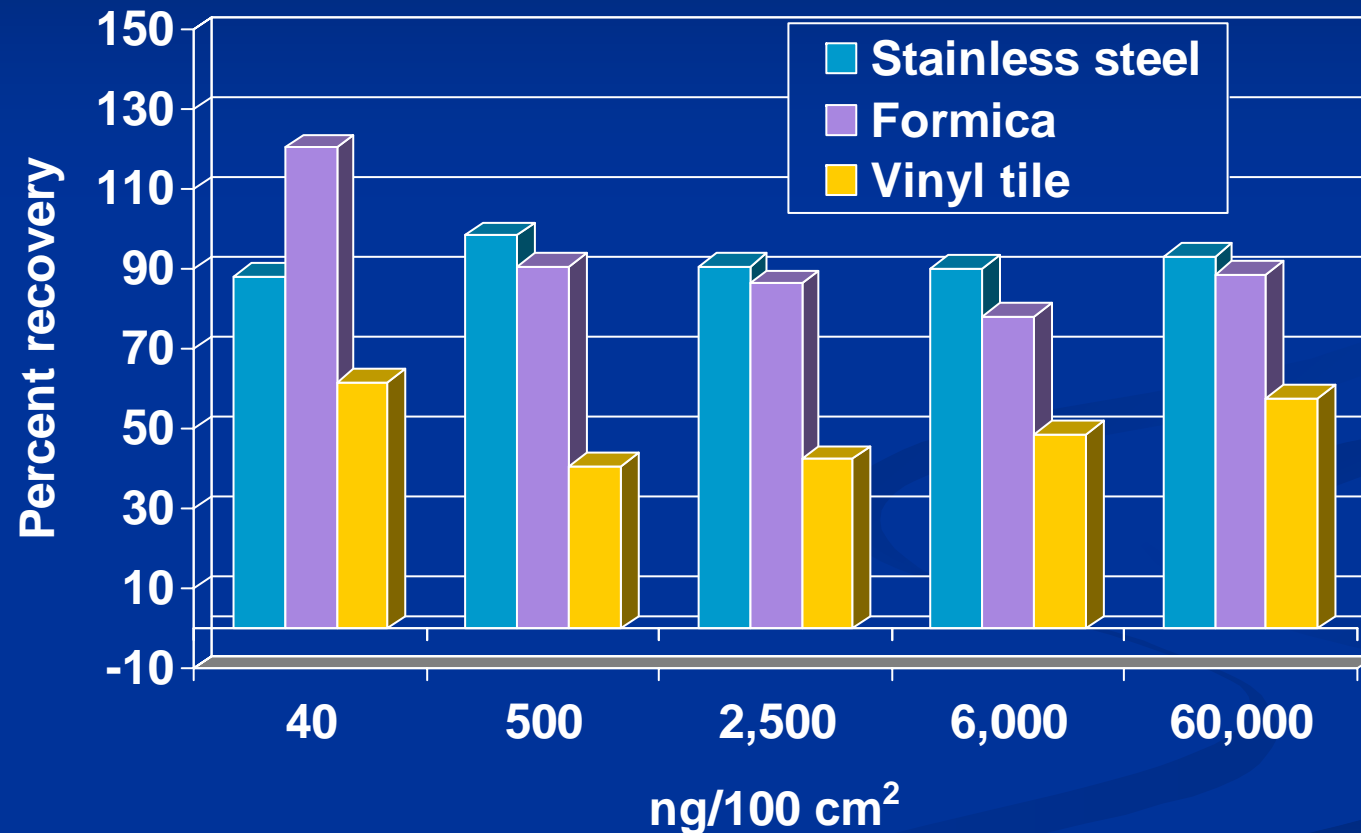
- Collision induced fragmentation yields unique product ions from precursors; permits unequivocal confirmation of analyte identity
- Often allows direct quantification in sample media – extraction for cleanup & pre-concentration become optional
- Separation of compounds via LC improves MS detection performance

Analytical Method

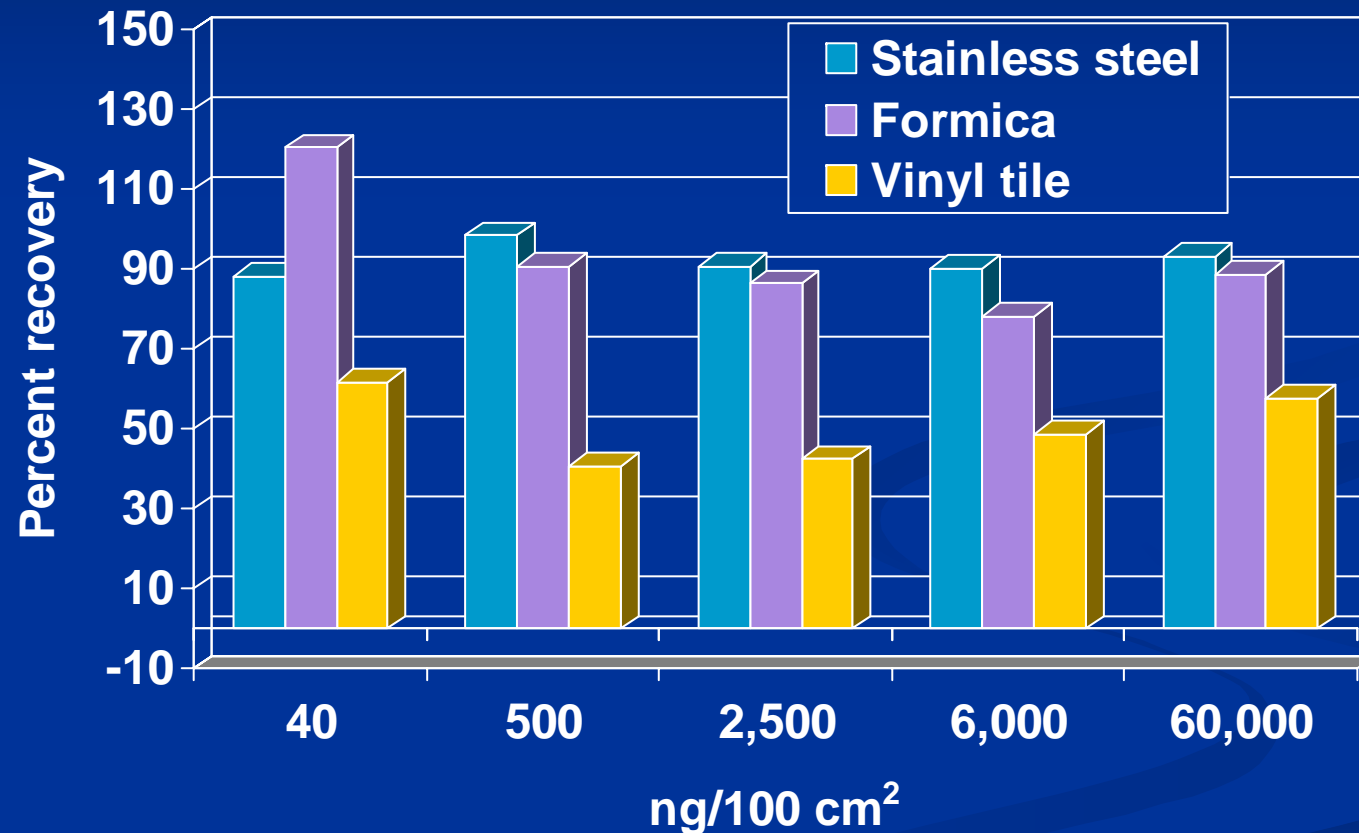
- LC-MS: 10 μL injections onto C_{18} reverse-phase column; mobile phase NH_4Ac or NH_4F buffer/Methanol as required (pH 4.2 – 6.0)
- Each sample analyzed in triplicate, quantification vs. linear regression plot from calibration standards



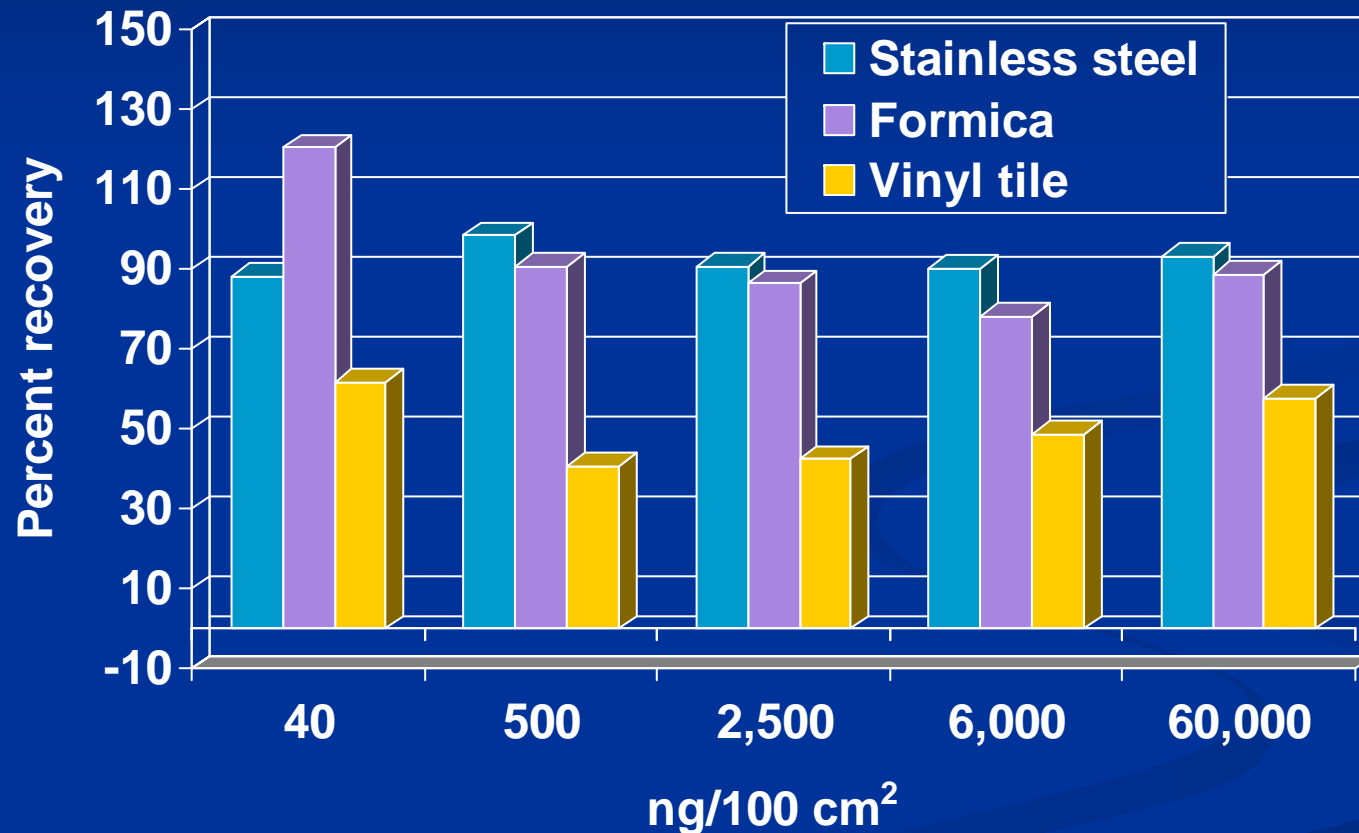
Recovery of cyclophosphamide from various materials (N=5)



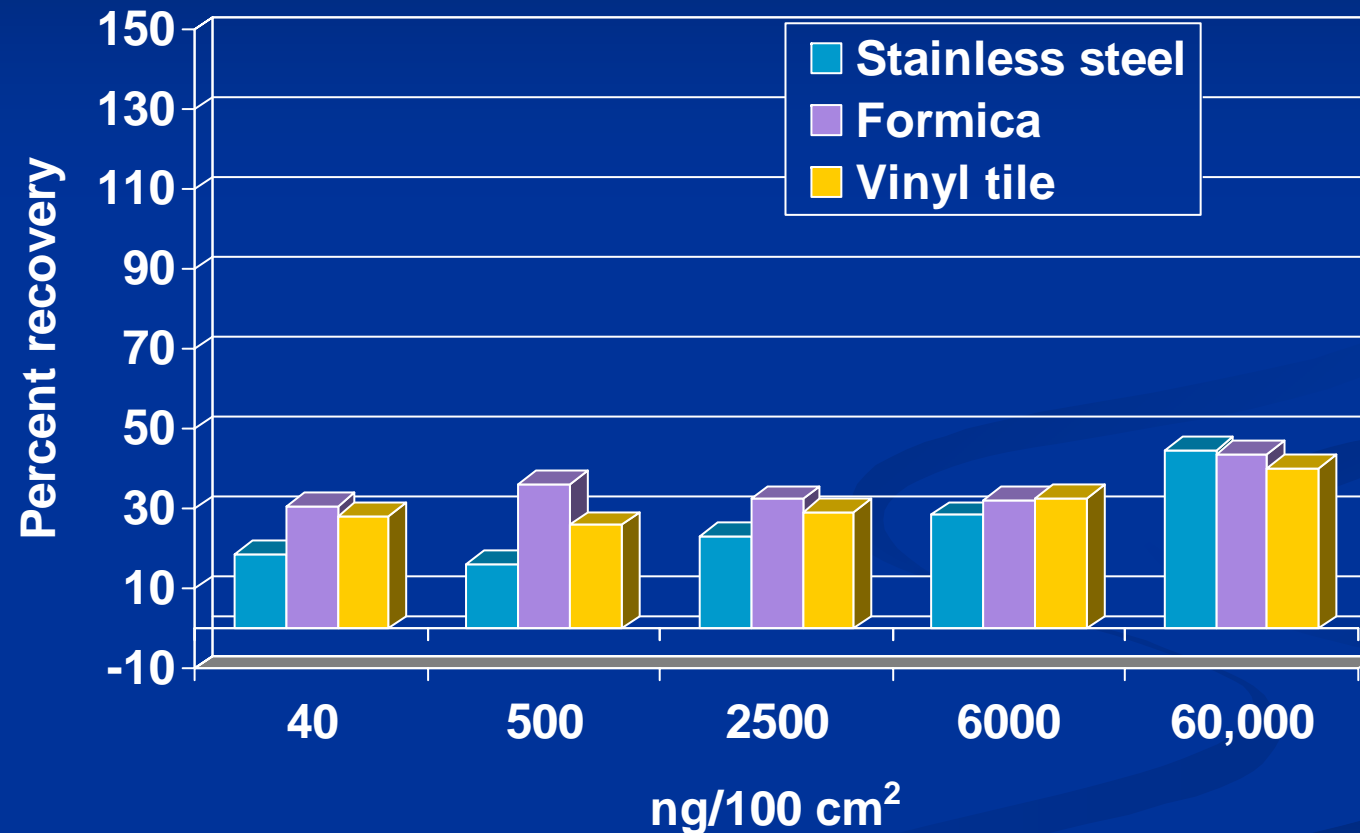
Recovery of fluorouracil from various materials (N=5)



Recovery of paclitaxel from various materials (N=5)



Recovery of doxorubicin from various materials (N=5)



NIOSH Healthcare Worker Study

- Comprehensive study of healthcare workers who handle antineoplastic drugs in three US hospitals
- Environmental sampling
- Biological sampling
- Health and work history
- 6-Week drug handling diary

Wipe Sampling Surfaces

- Biological safety cabinets/Isolators
- Airfoils of BSC
- Floors
- Count tops
- Transport containers
- Patient tables/chairs
- Patient restrooms
- Waste containers



Wipe Sample Field Studies



Number of Drug Handling Events

	Site 1		Site 2		Site 3		Total
Drug	Pharmacy	Nursing	Pharmacy	Nursing	Pharmacy	Nursing	
Cyclophosphamide	78	26	120	21	339	52	636
Ifosfamide	9	3	51	3	77	37	180
5-Fluorouracil	33	21	71	0	479	68	672
Paclitaxel	199	114	246	1	841	79	1480
Doxorubicin	119	61	135	14	394	69	792
Cytarabine	62	38	93	41	58	12	304
All others	658	496	1450	94	2384	653	5735
Total	1158	759	2166	174	4572	970	9799

LODs and Ranges for Sampled Drugs

Drug	LOD (ng/cm ²)	Mean (ng/cm ²)	Range (ng/cm ²)
Cyclophosphamide	0.11	17.3	0.11 - 288
Ifosfamide	0.10	1.57	0.10 - 19.8
5-Fluorouracil	0.07	34.0	0.11 - 910
Paclitaxel	0.07	0.36	0.08 - 2.97
Doxorubicin	0.22	1.50	1.5 (one >LOD)
Cytarabine	0.20	11.3	1.0 - 21.3

Detection Frequency for Surface Wipe Sampling by Drug

	Site 1		Site 2		Site 3		Percent
	Pharmacy	Nursing	Pharmacy	Nursing	Pharmacy	Nursing	
Cyclophosphamide	6/28	0/22	18/23	1/13	6/33	0/26	21.4
Ifosfamide	5/28	0/22	10/23	1/13	10/33	8/26	23.5
5-Fluorouracil	2/28	0/22	7/23	0/13	11/33	9/26	20.0
Paclitaxel	0/28	0/22	8/23	0/13	13/33	3/26	16.5
Doxorubicin	0/28	0/22	0/23	0/13	0/33	1/26	0.7
Cytarabine	2/28	0/22	3/23	0/13	0/33	0/26	3.5