

Review Article

The Transport of Chemicals in Semen

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Three mechanisms have been proposed for exposure of the conceptus to chemicals in semen: access of chemicals to the maternal circulation after absorption from the vagina, direct chemical exposure of the conceptus following transport from the vagina to the uterine cavity, and delivery to the egg and subsequent conceptus of chemical bound to the sperm cell. We review published data for each of these three mechanisms. Human seminal fluid chemical concentrations are typically similar to or lower than blood concentrations, although some antimicrobial agents achieve higher concentrations in semen than in blood. Vaginal absorption of medications has been shown to occur, although the vehicles in which these medications are delivered to the vagina may maintain contact with the vaginal epithelium to a greater extent than does semen. Assuming total absorption of a seminal dose of a chemical with a high semen: blood concentration ratio, distribution within the recipient woman would result in a blood concentration at least three orders of magnitude lower than that in the man. Direct delivery of seminal chemicals into the uterine cavity of humans has not been shown to occur, although it may occur in species such as the rat in which seminal fluid has access to the uterine cavity. Chemicals in or on human sperm cells have been demonstrated with respect to tetracycline and cocaine in vitro and aluminum, lead, and cadmium in vivo. The in vitro cocaine study offers sufficiently quantitative data with which to predict that oocyte concentrations would be five orders of magnitude lower than blood concentrations associated with cocaine abuse, assuming a maximally cocaine-bound sperm were capable of fertilizing. Thus, even using liberal assumptions about transmission of chemicals in semen or sperm, predicted exposure levels of a pregnant woman or of the conceptus are three or more orders of magnitude lower than blood concentrations in the man whose semen is the putative vehicle for chemical transport. *Birth Defects Res B* 74:119–131, 2005. © 2005 Wiley-Liss, Inc.

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INTRODUCTION

The question of paternally-mediated developmental toxicity has been much discussed in recent years. Much work and commentary in this area has been directed to chemical effects on the paternal genome or on epigenetic phenomena, but another area of interest is the transfer of chemicals in semen as a possible route of conceptus exposure. It is this transfer of chemicals in semen that will be discussed here.

There are three mechanisms that have been proposed for exposure of the conceptus to chemicals in semen:

1. Access of chemicals to the maternal circulation after absorption from the vagina, either at the time of conception or during an established pregnancy.
2. Direct chemical exposure of the conceptus following transport from the vagina to the uterine cavity.
3. Delivery to the egg and subsequent conceptus of chemical bound to the sperm cell.

Here, we review the data on these proposed mechanisms of exposure. Previous reviews (e.g., Mann and Lutwak-Mann, 1982; Pichini et al., 1994) have dealt with

isolated aspects of semen-mediated exposures; however, we propose to synthesize the literature on a broader array of these exposure issues.

THE SOURCE AND COMPOSITION OF SEMEN

Semen consists of spermatozoa and seminal fluid. Spermatozoa are produced in the seminiferous tubules of the testis and undergo additional maturation in the epididymis. Most of the liquid component of semen is comprised of secretions from the seminal vesicles and the prostate. Epididymal and vas deferens secretions account for a small portion of seminal fluid volume. Access of chemicals to the lumen of the seminiferous tubule requires crossing the so-called blood-testis barrier, which is composed of tight junctions between Sertoli cells. There is no consensus on the general purpose and

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effectiveness of this barrier, but with regard to access of chemicals to the ejaculate, the point may be moot. Chemicals in semen are believed to get there chiefly by way of the prostate and seminal vesicles.

The concentration of a chemical in semen will reflect the concentration of the chemical in blood and the customary determinants of drug distribution in different compartments, such as ionization and lipid solubility (reviewed by Pichini et al., 1994) are believed to be involved. Pichini et al. (1994), observed that the Henderson-Hasselbach equation would be expected to govern distribution of chemicals between blood and semen. The Henderson-Hasselbach equation is:

$$\text{pH} = \text{pK}_a + \log \frac{[\text{ionized chemical}]}{[\text{un-ionized chemical}]}$$

where pH refers to the compartment of interest, pK_a is the inverse logarithm of the dissociation constant for the ionization reaction and the bracketed terms refer to the concentration of ionized or un-ionized forms of the chemical in the compartment of interest. The pK_a of a chemical is a property of that chemical and represents the pH at which the chemical is half ionized (i.e., $[\text{ionized chemical}]/[\text{un-ionized chemical}] = 1$, $\log 1 = 0$).

Assuming that the concentration of un-ionized chemical is the same on both sides of a semipermeable membrane, the Henderson-Hasselbach equation can be used to predict the ratio of total chemical concentration (un-ionized+ionized) between two compartments. Taking C_p as the concentration of total chemical in prostatic fluid, for example, and C_b as the concentration of total chemical in a man's blood, for a weak base

$$\frac{C_p}{C_b} = \frac{1 + 10^{(\text{pK}_a - \text{pH}_p)}}{1 + 10^{(\text{pK}_a - \text{pH}_b)}}$$

where the pH of the prostatic and blood compartments are designated by their respective subscripts.

If the pH of blood (pH_b) is 7.4, and the pH of prostatic fluid (pH_p) is 6.6, the ratio of prostatic fluid and blood concentrations of the antibiotic clindamycin (for which $\text{pK}_a = 7.6$) can be calculated as 6.94. Pichini et al. (1994) observed, however, that calculations using this equation do not usually result in close concordance with observed semen concentrations. The discrepancies may be due to the relative contributions of the prostate, which produces an acidic fluid, and the seminal vesicles, which produce an alkaline fluid. These relative contributions may differ from one chemical to the next. In addition, transport of a chemical will be influenced by protein binding and lipid solubility. For clindamycin, the measured semen:plasma ratio is 11.3 (Pichini et al., 1994).

THE PRESENCE OF CHEMICALS IN SEMEN

A number of studies have documented the presence of environmental or medicinal chemicals in semen, and some studies have measured semen and blood concentrations in the same individuals. Table 1 presents many of the studies that have been conducted in men, and includes the measurements summarized by Pichini et al. (1994) as well as measurements published since the appearance of that review. A survey of Table 1 suggests that for most compounds, seminal concentrations are lower than blood, serum, or plasma concentrations. The notable exceptions to this generalization are

the chromium results of Bonde and Christensen (1991), results for xylenes published by Xiao et al. (1999, 2001), and the results for several antimicrobial agents, reproduced from Pichini et al. (1994).

The study of Bonde and Christensen (1991) involved men with chromium exposure through welding activities. The report indicates that biologic samples were "delivered outside the working room after change of dress and washing of hands and arms." The report does not address an assessment of ambient chromium concentrations outside the "working room," but presumably still in or near the workplace. The authors characterize the high seminal chromium content in workers as inconsistent because there was no difference in the exposure characteristics of men with low and high seminal chromium (the range of concentrations was 2 to 3908 mM in one subset of workers). The authors considered contamination of semen during the delivery process to be a likely explanation for the findings.

Xiao et al. (1999, 2001) evaluated men exposed to workplace xylene atmospheres up to 133.1 mg/m^3 . Semen samples were collected on site, and there was no information on the possibility of xylene contamination of semen during and after collection. Xylene was measurable in 11 of 24 blood samples and 10 of 17 semen samples. Results were presented in the original papers (and in our Table 1) only for the samples with detectable levels. Geometric means and standard deviations were presented due to the large variation among concentrations. The ratio of semen:blood xylene presented in Table 1 is based on the geometric means of all samples with detectable xylene, recognizing that there are different numbers of blood and semen samples involved. A more accurate representation of the semen: blood ratio would use concentrations from semen and blood specimens obtained from the same men; however, the Xiao et al. (1999, 2001) reports do not present sufficient information for such a calculation. In the same paper, results from measurements of benzene and toluene give semen: blood ratios less than unity. The inconsistency of the xylene results with the benzene and toluene results and the possibility of contamination during and after collection raise the question of the reliability of these measurements.

The antibiotic studies cited by Pichini et al. (1994) include agents that were present in semen at up to 11 times the concentrations measured in blood. In some instances, the measurements were made in men with prostatitis and the inflammatory process may have contributed to medication entry into semen. The antimicrobial medications that were the subjects of these reports were developed because they gain access to tissues and biologic fluids and may not be representative of other chemicals.

VAGINAL ABSORPTION OF CHEMICALS

The vagina is comprised of three distinct layers including an outer fibrous layer, a middle muscular layer, and a surface epithelial layer. The epithelium of stratified squamous cells remains thin until puberty at which time the epithelium thickens under the influence of estrogen. Epithelial thickness has been reported as 200 to $300 \mu\text{m}$ (reviewed by Woolfson et al., 2000). Arterial blood flow to the vagina is from the vaginal artery, a

Table 1
Semen Chemical Concentrations in Men

Chemical	Subjects/exposure levels	Concentration			Ratio, semen: blood ^a	Reference
		Blood, plasma, or serum	Semen	µg/mL		
Phenytoin	Individual 21-49-year-old men on therapy	4.6	0.97	0.18	Swanson et al. (1978b)	
		7.6	1.34	0.20		
Benzene	Men occupationally exposed at least 1 year (n) 13/24 positive in blood, 12/17 positive in semen	9.8	0.33	0.16	Xiao et al. (1999, 2001)	
		11.4	2.32	0.21		
		17.4	2.76	0.03		
		17.7	2.91	0.07		
		17.8	1.18	0.16		
		18.5	2.97	0.32		
		19.1	6.03	0.16		
		13.8 ± 5.5	2.31 ± 1.69	0.17 ± 0.08		
		mM, Geometric mean (range), positive samples only				
		4.40 ± 0.63 µM	1.85 ± 0.38 µM	0.42		
(0.40-51.32)	(0.17-8.54)					
1.42 ± 0.30 µM	0.22 ± 0.19 µM	0.15				
(0.30-17.17)	(0.11-0.40)					
1.32 ± 0.19 µM	5.67 ± 0.28 µM	4.30				
(0.38-4.50)	(1.12-33.84)					
Lead	81 smelter workers. Divided in quartiles based on blood lead	9.9	2.1	0.21	Alexander et al. (1998)	
		17.3	1.4	0.08		
		23.8	2.4	0.10		
		40.9	2.1	0.05		
		18.7	0.3	0.02		
		21.1	0.7	0.03		
		25.8	1.4	0.05		
		25.8	5.6	0.22		
		nM, mean ± SD (median; range)				
		17.31 ± 11.9	672 (260; 2-2830)	38.8		
17.25 ± 10.35	365 (18; 2-3908)	21.2				
14.46 ± 10.48	26 (11; 15-39)	1.8				
8.77 ± 2.65	280 (24; 9-1063)	31.9				
8.17 ± 2.46	16 (19; 2-93)	2.0				
µg/L, median (range)						
0.46 (0.19-1.49)	0.54 (0.17-1.67)	1.17				
0.68 (0.29-1.49)	0.62 (0.30-1.67)	0.91				
0.42 (0.19-1.05)	0.48 (0.17-1.09)	1.14				
4.33 (0.49-13.33)	0.85 (0.29-3.56)	0.20				
(pg/2-mL extract)						
	98.8					
	1,122.0					
Hexavalent Chromium	Divided in quartiles based on semen lead	≤ 0.5 (n = 21)			Bonde and Christensen (1991)	
		0.5-0.9 (n = 20)				
		0.9-1.8 (n = 20)				
		≥ 1.8 (n = 20)				
		Manual arc, stainless steel (n = 19)				
		Tungsten gas, stainless steel (n = 29)				
		Mild steel (n = 29)				
		Never-welded metal workers (n = 12)				
		Never-welded electricians (n = 16)				
		120 men, by smoking status				
Nonsmokers (n = 42), median age 29 (20-41)						
Former smokers (n = 9), median age 30 (27-38)						
Never smokers (n = 33), median age 28 (20-41)						
Smokers (n = 78), median age 31 (20-43)						
8 infertile mechanics						
1						
2						
Trichloroethylene					Forkert et al. (2003)	

Table 1
Continued

Chemical	Subjects/exposure levels	Concentration			Reference
		Blood, plasma, or serum	Semen	Ratio, semen: blood ^a	
Chloral	3		641.0		
	4		5,419.0		
	5		20.4		
	6		194.0		
	7		1,618.0		
	8		673.0		
	Median (interquartile range)		657 (146.4–1370)		
	1		62.7		
2		510.0			
3		1739.0			
4		69.1			
5		108.0			
6		119.0			
7		116.0			
8		61.2			
Median (interquartile range)		112 (65.9–314.5)			
Trichloroethanol	1		16.2		
	2		9.4		
	3		10.8		
	4		25.5		
	5		14.7		
	6		3.5		
	7		2.7		
	8		3.2		
Median (interquartile range)		10.1 (3.35–15.45)			
Dichloroacetic acid	1		<100		
	2		<100		
	3		<100		
	4		<100		
	5		<100		
	6		<100		
	7		5504		
	8		<100		
Ciprofloxacin	By hours after a 750-mg dose		mg/L, median (range), whole ejaculate		Naber et al. (1993)
	4 (n = 8)		0.87 (0.48–1.32)	8.4 (3.7–9.4)	
	12 (n = 6)		0.22 (0.09–0.52)	9.2 (7.8–18.7)	
	4 (n = 7)		mg/L, median (range), seminal fluid		
	12 (n = 5)		0.86 (0.48–1.10)	7.7 (5.4–8.1)	
	7 men sampled at different times after dosing		0.20 (0.09 ± 0.52)	6.6 (5.1–19.1)	
	Subject 3, 2 hours		2.29	0.12	
	Subject 5, 1.5 hours		1.80	0.1	
1 hour		3.98	0.18		
Aspirin					Kershaw et al. (1987)

Salicylic acid	Subject 6, 0.5 hours	9.66	0.31	0.03
	0.5 hours	7.78	0.33	0.04
	0.75 hours	6.23	Not detectable	0
	Subject 7, 0.5 hours	8.24	0.95	0.12
	0.5 hours	9.25	0.81	0.09
	0.75 hours	5.55	0.82	0.15
	The same 7 men, sampled after dose of aspirin			
	Subject 1, 4 hours	47.7	6.12	0.13
	12 hours	5.9	0.81	0.14
	Subject 2, 3 hours	43.5	8.63	0.20
	Subject 3, 2 hours	43.6	4.42	0.10
	9 hours	15.4	1.88	0.12
	Subject 4, 1.5 hours	43.0	5.08	0.12
	9 hours	15.5	1.93	0.12
	Subject 5, 1 hours	29.1	3.64	0.13
	6 hours	32.3	5.12	0.16
	Subject 6, 0.5 hours	27.4	4.82	0.18
	0.5 hours	23.6	2.70	0.11
	0.75 hours	28.3	2.15	0.08
	5 hours	31.4	5.85	0.19
	6 hours	32.6	4.62	0.14
	6 hours	27.8	6.05	0.22
	Subject 7, 0.5 hours	32.3	5.78	0.18
	0.5 hours	44.6	7.44	0.17
	0.75 hours	52.0	7.27	0.14
	5 hours	43.1	7.24	0.17
	6 hours	42.6	6.15	0.14
	6 hours	34.6	5.74	0.17
	From Pichimi et al. (1994) (concentrations in mg/L)			
Ampicillin	1 g by mouth	1.2	0.55	0.45
Methicillin	4 g intramuscularly	2.87	26.76	9.33
Cefalexin	1 g by mouth, split ejaculate	1.26	4.7, 5.2	3.7, 4.1
	1 g by mouth		4.7	
	1 g intramuscularly		6.9	
Cefalothin	2 g intramuscularly	2.71	9.64	3.55
Cefpodoxime	200 mg by mouth, HPLC measurements	0.12	0.14	1.16
	Bioassay measurements, median (range)	2.28	0.95	1.03 (0.24-1.86)
Erythromycin	1 g by mouth	4.58	0.66	0.14
Josamycin	2 g twice daily × 4 days then 1 g on the last day by mouth, split ejaculate 2 hours after last dose		2.23 ± 1.8, 1.56 ± 1.37	
Demeclocycline	600 mg by mouth	1.87	2.15	1.15
Doxycycline	200 mg by mouth	1	1	1
Tetracycline	1 g by mouth	2.99	4.08	1.36
Chloramphenicol	2 g by mouth	5.4	2.2	0.41
Thiamphenicol	0.5 g by mouth, sampling 2 hours later, mean	5.3	2.3	0.57
	0.5 mg every 8 hours × 3 doses, mean (range)	7.3	13.9	1.91 (0.86-4.4)
Ciprofloxacin	200 mg intravenously	0.44	2.53	5.8
	500 mg by mouth	0.9 ± 0.18	5.1 ± 1.42	5.6
Enoxacin	400 mg/day by mouth for 7-17 days		2.60	
	600 mg/day by mouth for 7-17 days		3.65	

Table 1
Continued

Chemical	Subjects/exposure levels	Concentration			Reference
		Blood, plasma, or serum	Semen	Ratio, semen: blood ^a	
Fleroxacin	428 mg intravenously, split ejaculate 400 mg by mouth	1.24 3.41	2.54, 3.47 5.80	2.0, 2.8 1.7 (prostatic fluid)	
Nalidixic acid	4 g by mouth	17.94	10.89	0.6	
Norfloracin	400 mg by mouth × 2 (separated by 12 hours)	0.89 ± 0.59	4.78 ± 2.69	5.4	
Ofloxacin	400 mg/day by mouth × 3.5 days, split ejaculate 800 mg by mouth	4.08 ± 0.36	2.44, 2.5 10.65 ± 3.36	2.6	
Pefloxacin	400 mg by mouth, split ejaculate		8.7 ± 1.2, 9.8 ± 1.1		
Sulfasalazine	3 g by mouth	16.16	0.9	0.05	
Aztreonam	1 g intramuscularly, prostatitis patients 1 g intramuscularly, healthy volunteers	18.04 ± 7.69 16.16 ± 8.42	1.8	0.10	
Clindamycin	300 mg by mouth, split ejaculate	1.10	10, 12.5	0.06	
Colistimethate	300 mg intramuscularly	1.99	0.88	11.3	
Kanamycin	1 g intramuscularly	25.41	6.64	0.44	
Metronidazole	500 mg by mouth	8.7	7.0	0.26	
Novobiocin	1 gram by mouth	17.15	14.64	0.8	
Trimethoprim	160 mg by mouth			0.85	
Carbamazepine				≥ 1	
Phenytol ^b	411 ± 117 mg by mouth	13.8 ± 5.5	2.31 ± 1.69	0.4–0.7	
Valproic acid	500 mg by mouth	25.9	1.98	0.17	
Cyclosporin	3.7–5 mg/kg intravenously	51–133	29–165	0.07	
Amitodarone	200 mg by mouth	1.13	0.37	0.5–1.2	
Proporanolol	80 mg by mouth	0.067 ± 0.021	0.058 ± 0.013	0.33	
Chloroquine	600 mg by mouth			0.9	
Aspirin ^b	975 mg by mouth			0.4 ± 0.06	
Mesalazine	1.5 g by mouth	5.18	0.62	0.12	
Salicylate	650 mg by mouth	70.75	0.04	0.2	
Methadone	52.9 mg by mouth	0.090 ± 0.009	0.155 ± 0.046	1.8 ± 0.6	
Amphetamine		0.110	0.054	0.5	
Caffeine	200 mg by mouth 400 mg by mouth	3.4 7.4		0.89	
Nicotine	19.47 ± 10.21 inhaled	0.05664 ± 0.00477	0.09306 ± 0.031	1.06	

^aRatio between semen concentration and blood, plasma, or serum concentration.^bPresented also in the first part of the table.

Table 2
Absorption of Medications From the Human Vagina

Chemical/dose	Indicator of absorption	Reference
Bromocriptine tablet 2.5 mg (9 women with galactorrhea)	Absorption inferred from decrease in mean \pm SD serum prolactin from 71.3 \pm 23.1 ng/mL before therapy to 10.6 \pm 3.2 ng/mL after 3 months of therapy	El-Mowafi et al. (2003)
Chlorhexidine 0.2% vaginal wash during labor, dose not quantitated (96 women)	Detectable blood levels in 34/96 women, highest mean concentration (\pm SEM) was 16.3 \pm 20.0 ng/mL	Nilsson et al. (1989)
Clindamycin phosphate 100 mg vaginal ovule or cream (13 healthy women, crossed over to each treatment)	4% of the cream and 30% of the ovule dose absorbed. Maximum serum concentration (ng/mL, mean \pm SD) 23.8 \pm 15.9 after the cream and 270 \pm 244 after the ovule.	Borin et al. (1999) Ritter et al. (1985)
Clotrimazole vaginal applications 200 and 500 mg	Plasma levels lower than detection level (0.01 μ g/mL). Absorption estimated at 3–10%	
Estrone or 17 β -estradiol, 0.5 mg placed as a solution in the vagina (10 healthy menopausal women)	Peak plasma estrone (mean \pm SEM) 208 \pm 39 pg/mL, 17 β -estradiol 860 \pm 247 pg/mL	Schiff et al. (1997)
Hexachlorophene 3% as lubricant for vaginal examinations during labor (total doses not measured) (28 women in active labor)	Maternal serum levels detected in 12/28, range 142–942 ng/mL Cord serum levels detected in 9/28, range 177–617 ng/mL	Strickland et al. (1983)
Itraconazole cream 5 g of 2% cream (100 mg) \times 3 days (8 healthy women)	All plasma levels below detection limit (1 ng/mL)	Francois et al. (2003)
Lysuride tablet-0.2 mg (9 women with galactorrhea)	Absorption inferred from decrease in mean \pm SD serum prolactin from 72.7 \pm 23.7 ng/mL before therapy to 12.0 \pm 5.7 ng/mL after 3 months of therapy	
Metronidazole vaginal tablets, 100 mg (16 healthy women)	Maximum serum concentration 433–1156 ng/mL	Hoffmann et al. (1995)
Miconazole 1,200 mg vaginal tablet (11 healthy women)	Maximum serum concentration (mean \pm SEM) 10.4 \pm 1.3 μ g/L. Absorption estimated at 0.3–2.1% of the administered dose.	Daneshmend, (1986)
Misoprostol 400 μ g tablet (5 pregnant and 5 non-pregnant women per route)	Peak serum concentration of metabolite (mean \pm SD) 165 \pm 86 pg/mL after vaginal dose, 277 \pm 124 pg/mL after oral dose; AUC higher after vaginal dose due to delayed but prolonged absorption.	Zieman et al. (1997)
Naproxen 500 mg suppository (5 healthy women)	Mean (\pm SEM) peak serum concentration 8.1 \pm 1.24 μ g/mL	Constantine et al. (1987)
Oral contraceptive containing 0.5 norgestrel and 0.05 mg ethinyl estradiol, placed vaginally each day for 1 month or taken orally each day for 1 month (cross-over design, 6 women)	Vaginal route resulted in lower plasma concentration of <i>l</i> -norgestrel during the first 24 hours. After 2 weeks, plasma concentrations did not vary by route of administration.	Alvarez et al. (1983)
Progesterone 100-mg vaginal suppository (10 menopausal women also on estradiol)	Maximum serum concentration 5.7–20.9 ng/mL	Archer et al. (1995)
Progesterone vaginal tablet 50 or 100 mg (25 menopausal women/dose)	Mean serum concentration (\pm SD): 25 mg dose 20.43 \pm 8.01 nM; 50-mg dose 31.61 \pm 12.62 nM	Levy et al. (1999)
Prostaglandin E ₂ 2–5 mg tablets (27 pregnant women for labor induction)	Peak plasma metabolite (15-keto-PGE ₂) 140–270 pg/mL	Gordon-Wright and Elder, (1979)
Providone-iodine vaginal disinfectant solution applied for 2 minutes. Dose not quantitated. (<i>n</i> = 12 nonpregnant women)	Total serum iodine levels increased 5 to 15-fold	Vorherr et al. (1980)
Terconazole vaginal cream 5 g of 0.8% cream (40 mg)	Daily mean peak concentration at 6.6 hours of 5.9 ng/mL; absorption 5–8% in 3 hysterectomized women and 12–16% in 2 women with uteri intact but with tubal ligation.	Package insert
Tioconazole vaginal tablet 300 mg (10 women with vaginal candidiasis)	Plasma concentrations (8-hour mean) 21.2 ng/mL, at 24 hours undetectable in 9/10 subjects	Houang and Lawrence (1985)
Tranexamic acid 300–350 mg via tampon (20 women)	Blood tranexamic acid concentrations 0.20–3.53 μ g/mL	Moodley et al. (1992)
Estrone 0.5 mg (menopausal women)	From 1983 review by Benziger and Edelson (1983) Plasma concentration 733 pg/mL	
Progesterone 50 or 100-mg suppository (menopausal women)	Mean peak serum concentration 13.5 ng/mL	
Medroxyprogesterone acetate 100 mg intravaginal ring	Plasma concentration 0.37–0.63 ng/mL	
Norgestrel 75 mg by mouth compared to 50 or 100 mg by vaginal ring	Serum concentrations 1.5–2 ng/mL after oral dose, 5–11 ng/mL after vaginal dose	
Norethindrone intravaginal ring, 50 or 200 μ g/day	Mean plasma concentrations 283 and 666 pg/mL on low and high-dose regimens, respectively	
Penicillin-100,000 to 300,00 unit suppository in non-pregnant, pregnant, and postpartum women	Absorption in pregnant women near term characterized as “very little.” Blood concentrations in	

Table 2
Continued

Chemical/dose	Indicator of absorption	Reference
Sulfanilimide 5 g dry powder	nonpregnant women with vaginitis were 0.66–0.69 units/mL. Postpartum blood concentrations were peaked at up to 1 unit/mL, although lower and frankly undetectable values were obtained in many women. Blood concentrations up to 14 µg/mL	

branch of the internal iliac (hypogastric) artery, which anastomoses with the pudendal and the uterine arteries. The venous drainage is via the internal iliac veins, which drain into the inferior vena cava, bypassing the hepatic portal system.

The vagina is normally collapsed, with the anterior and posterior walls in apposition. Pharmaceutical delivery systems developed for vaginal administration include suppositories, which are designed to be retained in the upper portion of the vagina behind the apposed vaginal walls, rings, or preparations with adhesive elements to promote retention in the vagina. Leakage limits the vaginal absorption of medications. For example, Abrams and Weintraub (1983) could recover only about 1% of vaginally administered miconazole from urine and feces over 7 days, the remainder presumably having leaked out of the vagina. Based on anecdotal experience, vaginal leakage of semen is common, although we have not seen studies quantitating this phenomenon. Human sperm are delivered in semen to the cervical mucus, into which ejaculation occurs. The sperm may be retained for days within the cervical crypts from which they are released into the upper genital tract. Seminal fluid itself does not enter the uterus; in fact, intrauterine insemination programs must use sperm washing or other procedures to separate the sperm from seminal fluid because seminal fluid contains antipacification factors and prostaglandins, which can cause severe uterine cramping (Carrell et al., 1998; Dodson et al., 1998).

The degree to which a chemical is absorbed from the vagina would be expected to depend on the chemical's molecular weight, lipophilicity, and degree of ionization. Ionization is likely to change as vaginal pH changes. Vaginal pH is low, but is transiently increased by semen and by the vaginal secretions that are produced during sexual arousal. We have not located data on systemic absorption of chemicals delivered to the human vagina in semen. There are, however, many studies on the systemic absorption of pharmaceutical products used in the vaginas of nonpregnant women (Table 2). Note that systemic blood or plasma concentrations in these studies not only reflect the degree of absorption but also the volume of distribution of the medication. Volume of distribution varies for different agents, depending on lipid solubility, plasma protein binding, and tissue binding. For a 70-kg nonpregnant human, blood volume is 5.5 L, extracellular fluid volume is an additional 12 L, and total body water is 42 L (Benet et al., 1990). Chemicals that are extensively tissue-bound may have apparent volumes of distribution that are considerably

higher than the total volume of the body, due to the appearance of only minute amounts of the chemical in the circulation. During pregnancy, plasma volume and total body water increase considerably, increasing volume of distribution for many compounds.

Table 2 includes studies performed in menopausal women. It is not clear that these studies are applicable to pregnant women inasmuch as the epithelium of the menopausal vagina is thinner than vaginal epithelium during the reproductive years.

SEMINAL DELIVERY OF CHEMICALS IN EXPERIMENTAL ANIMALS

Although some nonhuman primate females have been noted to permit coitus during early pregnancy, most experimental animal species do not mate after pregnancy has occurred. There are no experimental animal studies evaluating the delivery of chemicals to pregnant females through seminal fluid, although we identified three studies that evaluate vaginal delivery of chemicals through mating.

Ericsson and Baker (1966) presented a study in which male Sprague-Dawley rats were treated with estradiol 1 mg/day or vehicle subcutaneously for 8 days prior to mating. Females were killed 1, 2, and 3 days after mating. The authors concluded that estrogen had been transmitted to the female through coitus because uterine size was increased in females that had been mated to estradiol-treated males. Data in this paper appear to be presented for three females per treatment group on each of the first 3 days of pregnancy. The authors do not present statistical evaluations, but assuming $n = 3$, the mean \pm SEM uterine weight on the first day was 485 ± 33 mg in the estradiol group and 325 ± 5 mg in the control group ($p = 0.0012$, unpaired t test performed by us).

Swanson et al. (1978a) performed a study in rabbits designed to assess the transmissibility of methadone to the female via semen. There were two parts to the study. In the first part, five male rabbits were given 40 mg (about 10 mg/kg) methadone intramuscularly. Seminal methadone concentrations peaked at about 300 µg/mL. In the second part of the study, dialysis bags containing 40 mg methadone in 0.5 mL distilled water were secured into the vaginas of four female rabbits. Dialysis bags were used because instillation of as little as 0.1 mL of methadone solution into the vaginas of rabbits was associated with immediate expelling of the dose. A metal clip was placed over the vaginal introitus to prevent expulsion of the bag, which was left in the vagina for

90 minutes. Blood methadone in the females peaked at about $1\mu\text{g}/\text{mL}$. The authors concluded that they had shown high concentrations of methadone in the semen of rabbits and vaginal absorption of methadone. This conclusion is strictly correct, but we note that the vaginal absorption was under artificial circumstances (administration of the drug in a dialysis bag), using a methadone concentration in the dialysis bag of $80\text{mg}/\text{mL}$. The concentration in the dialysis bag was 267 times the maximum seminal concentration obtained after a very large ($10\text{mg}/\text{kg}$) intramuscular dose in male rabbits.

The only experiments we located in which there were quantitative estimates of transmission of a chemical from male to female animals during coitus were from the laboratory of Barbara Hales and Bernard Robaire (Hales et al., 1986; Robaire and Hales, 1994), and we will describe these studies in some detail.

In the first study (Hales et al., 1986), quantification was performed using ^{14}C -cyclophosphamide. Because the administered doses were reported in millicuries (mCi) and results were reported in disintegrations/minute (dpm), we converted the administered and measured amounts of cyclophosphamide into concentrations in blood, seminal fluid, and tissue, using $1\text{mCi} = 6.2 \times 10^5\text{dpm}$ and a cyclophosphamide molecular weight of 261.10. The administered cyclophosphamide had a specific activity of $52.5\text{mCi}/\text{mmol}$ and was ring-labeled (suggesting that metabolism would result in little loss of label). We calculated conversion of $3.25 \times 10^7\text{dpm}/\text{mmol}$ cyclophosphamide and 8ng cyclophosphamide/dpm in this study. We note that most of the cyclophosphamide given to the animals in these studies was unlabeled and our calculations pertain only to the small amount of labeled drug that was administered.

In the first experiment, adult male Sprague-Dawley rats weighing 250–300 g were given labeled cyclophosphamide at $50\mu\text{Ci}/\text{rat}$ ($0.95\text{nmol}/\text{rat} = 0.25\mu\text{g}/\text{rat}$ or a little less than $1\mu\text{g}/\text{kg}$ bw) plus unlabeled cyclophosphamide $10\text{mg}/\text{kg}$ bw. The cyclophosphamide was given into the jugular vein after which blood and seminal vesicle fluid were collected at intervals up to 120 minutes later. Plasma cyclophosphamide peaked at about $14 \times 10^{-5}\text{dpm}/\text{mL}$ ($1.12\text{fg}/\text{mL}$) with a rapid decrease to about $6 \times 10^{-5}\text{dpm}/\text{mL}$ ($0.48\text{fg}/\text{mL}$). Seminal vesicle fluid cyclophosphamide peaked at about $5 \times 10^{-5}\text{dpm}/\text{mL}$ ($0.40\text{fg}/\text{mL}$) (concentrations estimated from a figure).

In the second experiment, hormone-primed ovariectomized female rats weighing 200–225 g were mated to males that had been treated intraperitoneally 1 hour previously with the same cyclophosphamide regimen ($50\mu\text{Ci}/\text{rat}$ labeled drug plus $10\text{mg}/\text{kg}$ bw unlabeled drug). Three male rats were used in the experiment. After 5–10 minutes of cohabitation with a female, a second and third female were introduced at 2-hour intervals for each of the male rats. Females were killed 50 minutes after mating for evaluation of the seminal plug, vagina, cervix, uterus, kidneys, liver, spleen, and tibialis anterior muscle for radiolabeling. Males were killed 5 hours 20 minutes after cyclophosphamide treatment and label was quantitated in urine, seminal vesicle fluid, and serum. The highest counts in females were in the vaginal plugs, with first-mating plugs yielding mean \pm SEM counts of $20.34 \pm 3.02 \times 10^{-4}\text{dpm}/\text{g}$ ($16.3 \pm 2.4\text{pg}/\text{g}$ tissue). At the time of the third mating, 5 hours after

cyclophosphamide treatment of the males and just prior to killing of the males, seminal plug and seminal vesicle fluid counts were similar ($8.23 \times 10^{-4}\text{dpm}/\text{g}$ and $8.7 \times 10^{-4}\text{dpm}/\text{mL}$, respectively) as would be expected. After the first mating, when the seminal plug counts were the highest, the uterine muscle concentration of cyclophosphamide was $0.71 \pm 0.16 \times 10^{-4}\text{dpm}/\text{g}$ ($0.57 \pm 0.13\text{pg}/\text{g}$ tissue).

In a third experiment, 10 male rats/group were treated with cyclophosphamide in saline at 0, 10, 30, or $100\text{mg}/\text{kg}$ bw 1 hour before dark and cohabited overnight with two proestrous females per male. Sperm-positive females were killed 20 days later and uterine contents evaluated. Using the male as the statistical unit, implantations per pregnant female per male were significantly reduced at the $30\text{mg}/\text{kg}$ cyclophosphamide dose to 12.5 ± 0.7 from a mean \pm SEM of 14.7 ± 0.3 in the control group. There was no significant decrease in implantations per pregnant female per male in the $100\text{mg}/\text{kg}$ cyclophosphamide group. Calculating a preimplantation loss rate as the difference between number of corpora lutea and number of implantations as a percentage of total corpora lutea, there was a significant increase in preimplantation loss in the $100\text{mg}/\text{kg}$ cyclophosphamide group ($28/181 = 15\%$) compared to the control group ($19/221 = 9\%$); however, taking the treated male as the statistical unit, there was no significant difference in the difference between corpora lutea and implantations by treatment group. The authors noted that these results did not distinguish between a treatment effect on fertilizing ability of the sperm and an effect on preimplantation embryo viability. There were no effects of cyclophosphamide treatment on postimplantation loss or on embryo development.

In a subsequent study (Robaire and Hales, 1994), the investigators mated females to normal untreated males to establish pregnancy. The females were then remated within 2 hours to vasectomized males that had been treated intraperitoneally with cyclophosphamide in saline at 0, 50, or $100\text{mg}/\text{kg}$. When the difference between total implantations and total corpora lutea were analyzed as a percentage of total corpora lutea, there was a statistically significant difference between the rate of preimplantation loss in control females (3.6%) and that in the females exposed to cyclophosphamide-treated males (12.3 and 15.5% in the 50 and $100\text{mg}/\text{kg}$ bw groups, respectively; $p \leq 0.02$ by Fisher's Exact test with the pregnant female as the experimental unit). No analysis was provided using the treated male as the statistical unit, and each male was mated to two females (B. Hales, personal communication, October 7, 2004). There were no treatment effects on corpora lutea/pregnant female or implantations/pregnant female, suggesting that there may not have been a treatment effect using the treated male as the statistical unit.

In the three-dose study (Hales et al., 1986), the authors interpreted the deficit of implantations per corpus luteum per pregnant female per male as showing a decreasing trend, and this trend was displayed as a graph in a subsequent book chapter (Robaire and Hales, 1994). The mean \pm SEM percentage deficit in implantations per pregnant female per male for the 0, 10, 30, and $100\text{mg}/\text{kg}$ groups were 8 ± 3 ($n = 9$), 10 ± 3 ($n = 8$), 13 ± 5 ($n = 9$), and 15 ± 3 ($n = 9$) (analysis of variance [ANOVA] $p = 0.31$; linear trend test $p = 0.16$, statistics performed by us using GraphPad Prism software). Although we did

not confirm a statistically-significant dose-related effect of cyclophosphamide, especially when the treated male was considered the statistical unit, a similar deficit in implantations was shown in two studies. The replication of findings adds to the likelihood that the observed effect was real and that the lack of statistical significance was related to the small number of animals used in these studies. A deficit in implantations could have been due to impaired fertilization from sperm exposed to cyclophosphamide in the female genital tract rather than to early death of embryos after fertilization. The Hales and Robaire studies have been cited to support the proposition that chemicals given to males can be absorbed by females after coitus and can cause abnormalities of embryo development; however, these studies may show instead that cyclophosphamide introduced into the uterine cavity with sperm can cause reproductive impairment. The access of seminal cyclophosphamide to the uterine cavity may be critical to these findings and be an important difference between rats and humans.

ACCESS OF VAGINAL CHEMICALS TO THE UTERINE CAVITY

There are two mechanisms by which chemicals placed in the vagina have been proposed to reach the uterine cavity: 1) countercurrent transfer from the vessels draining the vagina to the uterine arteries, and 2) transport through the cervical canal.

The countercurrent mechanism involves the diffusion from venous and lymphatic vessels traveling back from the vagina towards the vena cava to the uterine arteries traveling in the opposite direction in anatomic proximity to the venous and lymphatic vessels. The countercurrent mechanism has been proposed to explain the observation that the administration of vaginal progesterone is followed by endometrial effects greater than those predicted based on systemic progesterone concentrations (reviewed by Cicinelli and de Ziegler, 1999). Intravaginal progesterone results in higher ratios of endometrial to serum progesterone concentration than does intramuscular progesterone administration (Cicinelli et al., 2000) and uterine artery progesterone concentrations are higher than simultaneous radial artery concentrations in women given vaginal progesterone (Cicinelli et al., 1998). In the study by Cicinelli et al. (2000), 90 mg of progesterone gel placed in the vagina gave rise to a mean \pm SD serum progesterone concentration of 4.82 ± 2.25 ng/mL and an endometrial progesterone concentration of 1.05 ± 0.67 ng/mg protein. We note that these data were obtained in menopausal women, and it is not clear that the data would apply to reproductive-age or pregnant women. In addition, we are not aware that the proposed countercurrent transfer from vaginal vessels to the uterine arteries has been demonstrated for chemicals other than progesterone and, possibly, 17 β -estradiol (Cicinelli et al., 2004).

Transfer of material through the cervical canal into the uterus clearly occurs with respect to spermatozoa. In humans, after spermatozoa are ejaculated, they reside in the cervical mucus for days, being released continuously into the upper genital tract. After ovulation, the cervical mucus becomes impenetrable to sperm. This effect is attributed to progesterone from the corpus luteum, and can be reproduced with pharmaceutical progestins

(Chretien et al., 1980). Mucus, generally-speaking, is composed of water, glycoproteins (chiefly mucin), and free proteins. The ultrastructure of cervical mucus has been studied in detail during different parts of the menstrual cycle and during pregnancy (Chretien, 1978). Pregnancy is associated with a tightening of the glycoprotein framework of the mucus, and this tightening of the mesh-like glycoproteins may produce a barrier to sperm and to microorganisms.

Principles of drug transfer through mucus have been reviewed by Khanvilkar et al. (2001); most empiric data are derived from gastrointestinal or respiratory tract mucus. We have not located data on transfer of chemicals through the cervical mucus of pregnancy. The observation that seminal prostaglandins do not enter the uterine cavity, even during the preovulatory period when mucus is highly penetrable by sperm, suggests that chemical transfer through cervical mucus may be impeded.

CHEMICALS BOUND TO SPERM

Sperm do not gain access to the uterine cavity during pregnancy, but they are present in the uterus and fallopian tube at the time of fertilization. One theoretical mechanism of chemical exposure of the conceptus is carriage of the chemical into the egg at the time of fertilization. Evidence for such a mechanism has been based on chemical adsorption to the sperm cell, and we will discuss each of the chemical adsorption studies.

Ericsson and Baker (1967) exposed rabbit, boar, and human sperm in vitro to tetracycline. Using fluorescence under ultraviolet and ultraviolet blue light as a marker of the presence of tetracycline, they determined that sperm heads and tails bound tetracycline and that qualitatively the fluorescence was retained after sperm washing. When rabbits were injected intravenously with tetracycline 25 mg/kg twice daily for 2 days, fluorescence appeared in sperm collected with an artificial vagina. There was no fluorescence in epididymal sperm, suggesting that the tetracycline exposure of sperm occurred through accessory gland secretions.

Two publications of Lutwak-Mann (Lutwak-Mann, 1964; Lutwak-Mann et al., 1967) are frequently cited as examples of putative thalidomide developmental effects mediated through sperm delivery of the chemical. The first report (Lutwak-Mann, 1964) is labeled a preliminary communication and recounts pregnancy outcomes after 40 matings of six male rabbits that received different oral doses of thalidomide for different lengths of time. Dose regimens included 2,500 mg/animal for 21 days, 750 mg/animal for 21 days, 900 mg/animal for 16 days, 1,300 mg/animal for 12 days, and 1,200 mg/animal for 10 days (one or two animals per dose regimen). It is not clear if the doses per animal were mg per day or mg cumulative dose for the entire treatment period, although it appears from a comment made in a subsequent study that these doses were cumulative. Matings occurred from 2–10 weeks following the treatment period. There were no control animals and statistical analysis was not applied. Of the 40 matings, there were three failures of pregnancy to occur, six litters of five or fewer offspring, and 16 litters with postnatal mortality. There were two kits with malformations, both born to the same male, in two different litters. In a subsequent report (Lutwak-Mann et al., 1967), additional matings after unspecified

doses to the males appear to have been added, bringing the total to 103 matings with 10 treated males and 90 females. In 18 matings, pregnancy failed to ensue, 12 litters contained a "low" number of offspring, in 25 litters, more than one-half the litter was lost by postnatal day 14, in 11 litters, the young were "grossly underweight," and in six matings, the young were malformed. The malformations are not enumerated per litter or per sire, but inasmuch as six different malformations were described, we assume that there were a total of six affected kits. The variety of dose regimens and the lack of detail on pregnancy outcome by sire prevent interpretation of these results.

Thalidomide was evaluated in seminal fluid and sperm using ^{14}C -labeled thalidomide administered to two male rabbits by mouth. A total of 244 mg/animal was given in two doses separated by 18 hours. Semen was collected at different intervals from the rabbits using an artificial vagina and radioactivity was measured in blood, seminal fluid, and spermatozoa separated by centrifugation (g value not given) and washed twice. Results were reported in μg thalidomide, so we assume the authors converted their counts based on specific activity; count and specific activity data were not reported. The highest concentrations reported were at 6 hours after dosing (the first time point measured) in rabbit A. The blood thalidomide concentration was 6.81 $\mu\text{g}/\text{mL}$, the seminal fluid thalidomide concentration was 9.60 $\mu\text{g}/\text{mL}$, and sperm thalidomide was 0.05 $\mu\text{g}/\text{mL}$. Sperm thalidomide was still detectable in this animal at 7 and 12 days at concentrations of 0.04 and 0.02 $\mu\text{g}/\text{mL}$, respectively. Seminal fluid thalidomide was reported as 0 on days 7 and 12 (limits of detection not given). In the second rabbit, sperm thalidomide was detectable only on day 1 at 0.02 $\mu\text{g}/\text{mL}$. On days 3 and 11, sperm thalidomide was reported as 0, although seminal fluid thalidomide was detected. Sperm counts were performed but not reported, so we cannot calculate the amount of thalidomide present per sperm cell. In a separate study, labeled thalidomide was mixed with rabbit semen *in vitro* and shown to be recoverable in twice-washed sperm.

Another frequently cited paper is that of Yazigi et al. (1991), which is often characterized as showing that cocaine is adsorbed by human spermatozoa without impairing their fertilizing ability. This report describes an *in vitro* study in which washed human spermatozoa pooled from two to four donors were incubated with radiolabeled cocaine with or without unlabeled cocaine (to estimated nonspecific binding). Specific binding was estimated in samples incubated at 4, 23, or 37°C for varying incubation periods at varying sperm densities. Motility was assessed by light microscopy, without automated methods, and viability was assessed by eosin exclusion. Cocaine binding was optimum at a temperature of 23°C and a sperm density of 80–120 $\times 10^6/\text{mL}$. The calculated dissociation constant (K_d) was 12.6 nmol/L and there were an estimated 3,600 binding sites per cell. Motility and viability were not affected by cocaine concentrations up to 670 μM . No other estimates of fertilizing ability were obtained.

A final paper on sperm concentrations of chemicals reported measurements of aluminum, lead, and cadmium in seminal fluid and spermatozoa of 27 men employed in a refinery or a polyolefin factory and 45

sperm donor candidates (Hovatta et al., 1998). Concentrations of the metals were lower in the seminal fluid and sperm of the occupationally exposed men than the sperm donors, attributed by the authors to good industrial hygiene practices and nonurban residence of the 27 workers. Measurements were made in ashed specimens and were expressed in milligrams per kilogram ($\mu\text{g}/\text{g}$). Combining the groups, cadmium was present in seminal fluid at a mean \pm SD concentration of $0.002 \pm 0.003 \mu\text{g}/\text{g}$, and in sperm at $0.04 \pm 0.005 \mu\text{g}/\text{g}$. Lead was present in seminal fluid at $0.03 \pm 0.02 \mu\text{g}/\text{g}$ and in sperm at $0.07 \pm 0.10 \mu\text{g}/\text{g}$. Aluminum was present in seminal fluid at $0.74 \pm 1.00 \mu\text{g}/\text{g}$ and in sperm at $1.93 \pm 3.37 \mu\text{g}/\text{g}$. Mean sperm concentration in the combined groups was $109 \pm 56 \times 10^6/\text{mL}$. There were no estimates of blood concentrations of the metals.

SYNTHESIS

Chemicals present in a man's blood can be present in his semen. Most chemicals for which there are data are present in semen at concentrations similar to or less than their concentrations in blood, plasma, or serum. Some antimicrobial medications appear to be concentrated in semen. Chromium and xylenes have been reported at higher concentrations in semen than in blood, but these data have been questioned based on the possibility of workplace contamination of semen specimens during and after collection.

Vaginal absorption of chemicals in humans has been demonstrated for a number of medications. The concentration of medication in the blood is expected to reflect the degree of absorption across the vagina and the volume of distribution for the medication. Medication data are typically obtained after the administration of preparations that are designed to remain in contact with the vaginal epithelium. Semen does not appear to be designed to remain in contact with the vaginal epithelium. Semen is deposited into the cervical mucus, which appears effective in the harboring of seminal fluid-free sperm for days; there are no data on whether chemicals in seminal fluid are retained in the human vagina or in the cervical mucus.

In spite of the uncertainties about how much semen would remain in contact with the vaginal epithelium for what length of time, it does not appear that vaginal exposure to chemicals in semen would be quantitatively important. This conclusion is based on the small amount of chemical that would be transferred by this route compared to the volume of distribution of the chemical. For example, clindamycin, which has the highest semen: blood ratio (11.3) of any of the medications in Table 1, was present in semen at a concentration of 12.5 mg/L (0.0125 mg/mL). The typical human ejaculate volume is 2–5 mL. If we assume that 5 mL of semen containing clindamycin 0.0125 mg/mL was completely absorbed by the vagina, the total absorbed dose would be 0.0625 mg. The volume of distribution of clindamycin in humans is 1.1 L/kg (Benet and Williams, 1990), or 66 L in a 60-kg woman. The expected blood concentration would, then, be 0.95 $\mu\text{g}/\text{L}$ (0.062 mg/66 L). The blood concentration in the man who contributed the semen was 1,100 $\mu\text{g}/\text{L}$ (Table 1). Thus, even for a medication that is concentrated more than 10-fold in semen, the expected blood exposure of a woman would be three orders of

magnitude lower than the blood exposure of the man who produced the semen.

It could be predicted, then, that a male's blood levels of a chemical would need to be extraordinarily high to produce a clinically important exposure of a female through semen. Such conditions may have been achieved by Ericsson and Baker (1966) in their treatment of male rats with estradiol 1 mg/day (3 or 4 mg/kg bw/day) subcutaneously. A typical dose of estradiol given to menopausal women is up to 0.1 mg/day (about 0.0017 mg/kg/day) transdermally. The dose of estradiol given to the male rats in the Ericsson and Baker (1966) study, then, was more than three orders of magnitude greater than the dose given to menopausal women on a body weight basis.

The demonstration in rats by Hales et al. (1986) of radiolabeling in the seminal plug, uterus, and other tissues of females mated to ^{14}C -cyclophosphamide treated-males confirms the principle that chemical transmission in semen can occur. The authors concluded that preimplantation loss was associated with seminal transfer of cyclophosphamide to the female, but a deficit between corpora lutea and implantations could just as likely have been due to impaired fertilizing ability of exposed spermatozoa as to poor viability of preimplantation embryos. Rat seminal fluid gains access to the uterine cavity and is held in the uterus by the copulatory plug. We do not know if these rat studies are relevant to species such as humans in which seminal fluid does not enter the uterine cavity. The only chemicals that have been shown to gain access to the human endometrium after vaginal placement are the naturally occurring hormones progesterone and 17β -estradiol, and these studies are from nonpregnant menopausal women (Cicinelli et al., 2000).

The attachment of some chemicals to human spermatozoa has been demonstrated in vitro. It is not known whether the fertilizing ability of sperm is affected by chemical binding. The one study that is often cited as evidence of unimpaired fertilizing ability (Yazigi et al., 1991) evaluated only crude in vitro measures of motility and viability, not fertilizing ability. This study estimated 3,600 cocaine binding sites per sperm cell at the optimum temperature of 23°C , well below normal testicular or epididymal temperature. If 3,600 molecules of cocaine were delivered by the sperm cell to the egg, the volume of which is 400 pL, the cocaine concentration within the egg would be about 15 pM (4.6 pg/mL) or about five orders of magnitude lower than blood concentrations of cocaine-abusing women. We have no information on possible effects of such low concentrations of cocaine on the egg or the early embryo.

As is so often the case in toxicology, the key issue in considering the transmission in semen of chemicals is the exposure level at the relevant target. Although there are few data in humans, the most generous estimates suggest concentrations in maternal blood or conceptual tissues three or more orders of magnitude lower than blood concentrations in the man whose semen is the putative vehicle for chemical transport.

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