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Excretion of methadone in sweat of pregnant women throughout gestation after controlled methadone administration

Allan J. Barnes, BS^a, Bertrand R. Brunet, PharmD, PhD^b, Robin E. Choo, PhD^c, Patrick Mura, PhD^d, Rolley E. Johnson, PharmD^{e,f}, Hèndrée E. Jones, PhD^g, and Marilyn A. Huestis, PhD^{a,*}

^aChemistry and Drug Metabolism, Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health, 251 Bayview Boulevard, Baltimore, MD 21224, USA

^bINSERM UMR 927, Université de Poitiers, Faculté de Médecine et Pharmacie, Rue de la Milétrie, BP 577, 86021 Poitiers, France

^cUniversity of Pittsburgh, Natural Sciences Department, Titusville, PA 16354, USA

^dLaboratoire de Toxicologie et Pharmacocinétique, Centre Hospitalier et Universitaire, Rue de la Milétrie, BP 577, 86021 Poitiers, France

^eDepartment of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD 21224, USA

^fReckitt Benckiser Pharmaceuticals Inc., Richmond, VA 23235, USA

^gDepartment of Psychiatry and Behavioral Sciences and Department of Obstetrics and Gynecology, Johns Hopkins University School of Medicine, Baltimore, MD 21224, USA

Abstract

Sweat patches (N=350) were collected throughout gestation from 29 opioid-dependent pregnant women participating in an outpatient methadone assisted therapy program. Volunteers provided informed consent to participate in Institutional Review Board-approved protocols. Methadone was eluted from sweat patches with sodium acetate buffer, followed by solid-phase extraction and quantification by GCMS (LOQ ≥ 10 ng/patch). Methadone was present in all weekly patches (N=311) in concentrations ranging from 10.2 to 12,129.7 ng/patch and in 92.3% of short-term patches (N=39, worn for 12 or 24 h) in concentrations up to 3303.9 ng/patch. Correlation between patch concentrations and total amount of drug administered ($r=0.224$), and concentrations and duration of patch wear ($r=0.129$) were both weak. Although there were large intra- and inter-subject variation in sweat drug concentrations, sweat testing was an effective alternative technique to qualitatively monitor illicit drug use and simultaneously document methadone medication assisted treatment.

Keywords

Sweat; Methadone; Therapeutic drug monitoring; Alternative matrix; Drug testing

*Corresponding author Marilyn A. Huestis, PhD Chief, Chemistry and Drug Metabolism IRP, National Institute on Drug Abuse, NIH 251 Bayview Boulevard, Room 05A-721 Baltimore, MD 21224 Tel.: +1 443 740 2524; fax: +1 443 740 2823 mhuestis@intra.nida.nih.gov.

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Introduction

Illicit opioid use in the context of complex social, physical and environmental factors is related to maternal and neonatal complications such as intrauterine growth restriction, pre-term delivery, low birth weight, decreased head circumference, meconium staining of the amniotic fluid, and fetal death.^{1–4} Methadone pharmacotherapy is an important component of comprehensive care available to pregnant opioid-dependent women. During pregnancy, methadone pharmacotherapy is more successful than medication-assisted opioid withdrawal in improving maternal treatment outcomes.⁵ Another tool in treating opioid-dependent patients is drug testing that monitors adherence to methadone medication assisted treatment and relapse to illicit drug use. Drug testing is a valuable means to monitor a patient's progression in treatment and deter illicit drug use. In addition, drug testing provides an objective surrogate measure of therapy effectiveness.

Urine analysis offers a short detection window of only two or three days, requiring monitoring of multiple specimens per week. Urine sampling also is considered invasive, and specimen adulteration is easily accomplished. Alternative matrices, such as hair, oral fluid and sweat, offer additional options to urine testing.^{6–8} Although sweat has been proposed as an alternative matrix for drug testing by the Substance Abuse Mental Health Service's Administration (SAMHSA)⁹, federal approval has not yet been achieved. The detection window of drugs in sweat is the time the patch is worn, usually 7 days, providing cumulative drug use data from patch application to removal.¹⁰

Few data are available on the excretion of methadone in sweat. In 1973, Henderson and Wilson detected methadone, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) and 2-ethyl-5-methyl-3,3-diphenylpyrroline (EMDP) in sweat from five methadone maintained patients; methadone was the primary analyte.¹¹ Other investigators also documented that methadone sweat concentrations far exceeded those of EDDP following methadone administration to 8 patients receiving 21.2–103.4 mg methadone daily for at least four weeks,¹² and to 10 patients receiving 20 – 90 daily for one week.¹³ In 20 methadone assisted treatment patients, there was no correlation between dose and methadone concentration in sweat; the R-enantiomer was the most abundant isomer.¹⁴

For the first time, we evaluated methadone excretion in sweat collected weekly throughout pregnancy in opioid-dependent women receiving methadone medication assisted therapy and specialized treatment. Multiple consecutive weekly patches permitted evaluation of dose-concentration relationships, and intra- and inter-individual variability. An additional pharmacokinetic study was conducted with short-term patches worn for 12–24 h.

Methods

Human participants

Opioid-dependent women aged 18–40, qualifying for methadone assisted treatment, and estimated gestational ages (EGA) 8–25 weeks, participated in a Center for Addiction and Pregnancy (CAP) study at the Johns Hopkins Bayview Medical Center (JHBMC). Women were required to meet the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for opioid dependence. Women resided at CAP during initiation of methadone treatment. Initial methadone dose was determined from self-reported frequency, magnitude and pattern of heroin consumption, clinical experience and data from the literature. None were prescribed methadone before study inclusion. Throughout gestation, participants received outpatient methadone medication assisted treatment, weekly individual and group counseling, transportation, child care, and specialized prenatal care. The JHBMC and the

National Institute on Drug Abuse Institutional Review Boards approved the research and participants provided written informed consent. A subset of women (N=7) received incentive vouchers (monetary rewards) for urine specimens that were negative for cocaine and opiates as part of a behavioral contingency management treatment study.

Specimen collection

Women visited CAP daily to receive methadone throughout gestation for a mean of 17.8 ± 6.3 (range 8–32) weeks. Sweat was collected with Pharmchek® sweat patches provided by Pharmchem, Inc. (Haltom City, TX). After thoroughly cleaning the skin with isopropyl alcohol, patches were applied to the back or arm. Sweat patches were generally worn for one week (range 2–24 days), but were dependent upon clinic attendance, and participation in the short-term pharmacokinetic study. Sweat patches had to remain on the skin, with no signs of tampering, in order to be included. After removal, patches were stored at -20°C until analysis. Number of patches per participant was dependent on gestational age at enrollment and adherence to scheduled appointments. Serial weekly patches were collected throughout study participation from enrollment through delivery and early post-partum.

Some women also participated in a short-term pharmacokinetic study, requiring residence on the General Research Center for 24 h. Two patches, one daily (0–24 h) and one short-term patch (0–12 h), were simultaneously placed prior to ingestion of the daily methadone dose. After twelve hours the short-term patch was removed and another applied (12–24 h). The amount of methadone excreted during the first 24 h was compared to amount excreted in the first and second 12 h exposure periods.

Analytical procedures

Methadone concentrations in sweat patch specimens were quantified according to a previously published gas chromatography mass spectrometry (GCMS) method that also included cocaine, benzoylecgonine, ecgonine methyl ester, anhydroecgonine methyl ester, heroin, 6-acetylcodeine, 6-acetylmorphine, codeine, and morphine.¹⁵

Drugs were quantified by linear regression with a 1/x weighting factor and 10 ng/patch limit of quantification. Two calibration curves were required due to a wide range of biomarker concentrations, and availability of only a single patch for analysis. The low curve's linear dynamic range was 10–1000 ng/patch; a high calibration curve (1000–10,000 ng/patch) was constructed for methadone by modifying GCMS injection techniques to extend the linear range. Estimates of imprecision were calculated from four replicate controls on five analytical runs (N=20) according to Krouwer.¹⁶ The pooled within-run component of imprecision, expressed as % coefficients of variation (%CV), was less than 3.9% at 15, 150, 750, 1500, 3000, and 8000 ng/patch. Between-run imprecision (%CV) at all concentrations was less than 3.2%. Total method imprecision was less than 4.6%. Recoveries at the same concentrations were $\pm 9.4\%$ of target.

Data analysis

Statistical processing (mean, median, standard deviation, range and correlation coefficient) of data was performed with GraphPad Prism V3.02 from GraphPad Software Inc., USA. The ability of two consecutive patches to detect a change in methadone dose was evaluated by determining whether methadone concentration in consecutive patches increased or decreased. Correlation coefficients (r) were determined between total and mean daily methadone dose and methadone patch concentrations and duration of patch wear. When possible, variables were grouped to obtain more information (e.g., same dose, all patches from one individual, and all patches worn the same duration).

For the short-term pharmacokinetics study, methadone concentrations in 24 h patches were compared to the sum of the 2 concentrations in the corresponding 12 h patches. To evaluate the time course of methadone excretion in sweat during the first 24 hours, percentages of methadone excreted during the first and second 12 h patches were compared to the corresponding 24 h patch. Hourly methadone excretion in 12 and 24 h patches were determined by dividing the administered methadone dose by the concentration of methadone in the patch and the number of hours the patch was worn.

Results

Human participants and clinical specimens

Twenty-nine pregnant opioid-dependent women (mean $\pm$ SD age 30.1 $\pm$ 5.3 years; range 19–40) between 9–29 weeks EGA participated in the study. Mean methadone dose at enrollment was 39.0 $\pm$ 13.9 mg/day (range 30–90), and at delivery, 78.1 $\pm$ 18.5 mg/day (range 30–110). Methadone concentrations in weekly patches (N=311) from 27 women were evaluated, and additionally, short-term patches (0–12, 12–24 and 0–24 h) from five women were included in the pharmacokinetics study. Two women only participated in the pharmacokinetics short-term study. Mean duration of patch wear was 6.9 $\pm$ 2.5 days (median 7; range 2–24). Mean number of sweat patches collected from each participant was 11.5 $\pm$ 6.2 (range 3–32). For the pharmacokinetic study, 39 short-term patches were collected from 5 women, allowing for comparison of 13 complete sets of patches.

Methadone concentrations in weekly sweat patches

Mean daily methadone dose was 66.1 $\pm$ 17.0 mg (median 70, range 10 to 100); mean dose administered during the patch wear period was 457.5 $\pm$ 216.5 mg (median 455, range 60–2150). Methadone was detected in all weekly sweat patches (N=311) with concentrations ranging from 27.0–12,129.7 ng/patch, with a mean concentration of 1650.0 $\pm$ 1669.0 ng/patch (median 1200.1).

Correlation between total methadone dose during patch wear and weekly methadone patch concentration was only 0.224. Weekly sweat patch concentrations had low correlations with total patch wear time (2–24 days; $r=0.129$) and with wear time when grouped, as shown in Table 1.

Intra-subject correlation coefficients (N=26) were determined for total methadone administered during patch wear and methadone concentrations in sweat patches. One patient was excluded, as she received the same methadone dose throughout the study. The mean correlation coefficient was only 0.359 $\pm$ 0.376 (median 0.395, range –0.272–0.974).

The ability of two consecutive weekly patches to detect a change in dose was evaluated. In only 75 of 150 consecutive patches (50%), were increases or decreases in dose reflected in matched increases or decreases in methadone patch concentrations. To minimize variability due to dose, we evaluated methadone sweat concentrations (N=49) in a subset of women (N=13) receiving equivalent daily methadone doses (70 mg) while wearing the patch 3–10 days (Table 2). Although identical doses produced similar mean, median and Cmax concentrations following different durations of patch wear, standard deviations were high. Further evaluation of patch wear duration (3–14 days) compared with equivalent daily doses (60, 70 or 80 mg) are presented in Figure 1. 24 patches from 8 subjects, 49 from 13, and 29 from 8 participants were collected for 3–14 days following equivalent methadone doses (60, 70 or 80 mg), respectively. There were no patterns of increasing concentration at any time point due to increased methadone dose. However, after the fourth day there was a linear relationship in mean concentrations from patches worn 5–12 days after receiving 60 mg

methadone. Interestingly, overall mean patch concentrations for this group were equivalent and appeared independent of dose or patch wear duration.

Excretion profiles of weekly patch concentrations (ng/patch) and weekly methadone dose (mg) from 3 representative subjects clearly demonstrate intra- and inter-subject variability (Figure 2). 13 weekly patches were collected from Subject F over 109 days (average wear period 8.4 days). Daily (62–75 mg) and weekly methadone doses (390–825 mg) produced concentrations in consecutive patches ranging from 181.1–379.6 ng/patch. Mean patch concentration throughout the study for Subject F was 294.1 ± 62.0 ng/patch. Despite dose and wear period changes, sweat patch concentrations were fairly consistent. More variability was noted in weekly patches (N=20) collected from Subject G over 178 days (average wear period 8.9 days). Methadone sweat excretion tended to decrease during the latter part of the study despite identical wear times (7 days) and weekly doses (490 mg). Methadone concentrations in 11 consecutive patches collected the last 94 days of the study decreased from 1907.9 (Patch 10) to 173.6 ng/patch (Patch 20). However, methadone concentrations increased from 2572.3 to 8333.6 ng/patch in patches (23–27) collected from Subject D maintained on an identical dose (70 mg) and identical wear time (7 days). Interestingly, even with similar daily methadone dose (57–90 mg), maximum weekly patch concentrations varied from 379.6 to 2770.7 to 9187.5 ng/patch, respectively, for Subjects F, G and D.

Pharmacokinetic study - Concentrations of methadone in hourly sweat patches

The short-term pharmacokinetic study was repeated at different stages of pregnancy, depending upon estimated gestational age at enrollment. Of five women participating in this portion of the study, 3 participated twice, 1 three times and 1 woman at four stages of gestation. One patch was worn the first 12 h after dosing, one 12 to 24 h after dosing, and one the first 24 h after dosing. Mean daily methadone dose was 75.8 ± 24.6 mg (median 80, range 20 to 100 mg). Methadone was quantified in 39 patches; 3 contained methadone below the limit of quantification. 36 patches contained 10.2–3303.9 ng methadone/patch. A detailed overview of methadone concentrations in hourly patches is presented in Table 3.

Median amounts of methadone excreted in 0–12 h and 12–24 h patches were similar, as 7 of the 0–12 h patches had higher concentrations, 5 lower, and in one pair methadone was not detected (Table 3). Despite similar C_{min} (13.2 and 10.2 ng/patch) and C_{max} (2047.1 and 2131.2 ng/patch) concentrations, there were up to 5 fold differences in corresponding 12 h patches. Weak correlations were observed when daily methadone dose was compared to patch concentrations in the first ($r = 0.424$) or second 12 h interval ($r = 0.449$).

Not surprisingly, concentrations of methadone in 24 h sweat patches were higher than in patches worn for 12 h. 24 h patches had higher methadone concentrations than 20 of 26 matched 12 h patches, with concentration differences up to 1256.8 ng/patch. However, the sum of the 0–12 and 12–24 h patches exceeded the methadone concentration in the matched 24 h patch in 8 of 13, or 61.5% of cases. Total amount of methadone (5243.4 ng/patch) excreted in 13 daily patches was only slightly higher than total methadone excreted in the same number of 0–12 h (3594.2 ng/patch) and 12–24 h patches (4909.4 ng/patch). Daily methadone excretion in sweat (0–24 h) was highly correlated ($r = 0.930$) to the sum of concentrations in corresponding 0–12 and 12–24 h patches; however, concentration differences between the individual sum of hourly patches (0–12, 12–24 h) and the corresponding daily patch (0–24 h) ranged from 8.6–1738.8 ng/patch.

Discussion

Sweat has been widely investigated over the last two decades as an alternative matrix for drug monitoring and appears useful for treatment, workplace, criminal justice, and child

custody applications,^{11, 17, 18} although clearly, we documented a lack of correlation between methadone dose and methadone sweat concentrations.^{19–22} Sweat testing documents compliance with pharmacotherapy while simultaneously revealing illicit drug use over a one-week period.^{12, 23} Extended detection windows, less adulteration potential, fewer clinic visits and continuous monitoring make sweat an intriguing alternative to urine testing for monitoring drug abuse. Sweat testing also has limitations. Sweat patch analysis is challenging as only one patch is available for extraction and different analytes may be present in a wide range of concentrations. Many validated GCMS methods are available,^{19, 20, 24, 25} for example, we recently developed a GCMS assay for methadone in sweat with an extended linear range (from 10 to 10,000 ng/patch) compatible with expected concentrations of methadone in weekly and hourly sweat patches.¹⁵

Our study population was pregnant heroin-dependent women, most of whom also abused cocaine. Women requested opioid agonist assisted therapy as part of comprehensive treatment that also included specialized prenatal care and individual and group counseling. Relapse to illicit drug use was identified by positive sweat results. For many participants, occasional heroin and frequent cocaine use was evident.²⁶ A few subjects reduced consumption of both drugs as delivery approached. Dosage increased regularly based on patient report and clinical assessments, explaining the wide range of methadone doses encountered in the study.

Weekly patches (N=311) contained a wide range of methadone up to 12,129.7 ng/patch. Henderson also reported similar variability in methadone sweat concentrations.¹¹ Sweat excretion is usually 500 mL/day but can reach 1000 mL/h in extreme conditions. Variability in methadone dose, sweat excretion, and metabolism or renal excretion rates, especially in pregnant women at different stages of gestation, may have contributed to the variability in methadone sweat patch content.²⁷ Excessive sweating is a side effect of methadone treatment that could also contribute to variability.²⁸ Others attempted to demonstrate a correlation between amount of methadone administered and methadone concentration in sweat. Kintz et al. reported a 0.014 r^2 for daily methadone dose and methadone concentration in 20 sweat patches from different individuals,¹⁴ while our research yielded a 0.224 (N=311) correlation coefficient, together suggesting that predicting methadone dose from sweat patch test results is not possible.

In addition, we evaluated the correlation between days a patch was worn to methadone sweat concentrations (N=311) during daily methadone dosing. A poor correlation ($r=0.129$) indicated that methadone concentration did not increase significantly with days the patch was worn. Skopp et al. reported similar results in a small number of patches.¹² The authors proposed that there was a loss of contact between the pad and skin after several days, or that methadone could be re-absorbed into the skin. They noted that methadone degradation was not responsible as the methadone to EDDP ratio was stable.

Furthermore, methadone sweat concentrations did not significantly change with increases or decreases in methadone dose; concentrations only reflected a dosage change 50% of the time. This is not surprising, since as demonstrated here in multiple ways, drug sweat excretion is qualitative rather than quantitative.^{12, 22} Overall, the variability in methadone excretion in sweat was remarkable. Inter-subject variability was extensive but variability within-subject also was large. Intra-subject correlations (N=27) for weekly methadone dose to methadone sweat concentrations were -0.272 – 0.974 . No pattern was evident, as some participants had methadone sweat concentrations that strongly correlated with dose ingested while others exhibited a weak relationship; poor correlations were not associated with the presence of illicit opiates or cocaine.

A drawback of sweat analyses is that the amount of sweat collected is unknown. Recent studies explored the possibility of finding a biological marker for calculating the amount of sweat collected. Potassium and sodium were investigated, but sodium was the better internal standard for amount of sweat excreted.²⁹ However, these data were for short-term patches worn only for 3 h. It is unknown if sodium would be as accurate a biomarker for patches worn for one week. The same authors recently reported a new application employing sodium to correct for the amount of sweat excreted in ethylglucuronide quantification.³⁰

Short-term patches (N=39) from five women evaluated the excretion of methadone in sweat during the first 24 h after administration (Table 3). Thirteen complete sets of patches (0–12, 12–24 and 0–24 h) were analyzed. The correlation between methadone sweat concentrations in these short-term patches and daily methadone dose was low ($0.365 < r < 0.449$), but better than the correlation observed with weekly patch concentrations and administrations. Correlations were only slightly higher for the 0–12 and 12–24 h patches ($r=0.424$ and 0.449) than for patches worn 0–24 h ($r=0.365$). Despite wide differences in methadone concentrations in short-term patches, there was an unexpected strong correlation for the sum of 0–12 h and 12–24 h patches to 24 h concentrations ($r=0.930$).

After controlled administration of 3,4-methylenedioxymethamphetamine (MDMA), concentrations in two consecutive 12 h patches (0–12, 12–24 h) and three short-term patches (0–6, 6–12, 12–24 h) were compared to the first daily patch (0–24 h). The daily patch usually was the most concentrated.³¹ In contrast, following methamphetamine administration, cumulative short-term patch concentrations were usually greater than those in the weekly methamphetamine patch.²¹ Schwilke et al. also observed that after controlled codeine administration, the sum of codeine excreted in hourly sweat patches was generally higher than concentrations in the corresponding weekly patch.¹⁹ However, large inter-individual variability in patch concentrations during these studies documented that patches worn longer do not always contain more analyte.

Some possible explanations for this variability are differences in bioavailability and metabolism between individuals and variations in sweat excretion rates. Also, changes occurring at different stages of pregnancy also may have contributed. Other possibilities are loss of drug through degradation on the patch or skin to analytes that are not monitored, re-absorption into stratum corneum or loss of analytes through the patch as hypothesized by Uemara et al.³²

In order to minimize dose variability, we evaluated weekly patches (N=49) from women (N=13) receiving identical 70 mg daily doses. Mean concentrations from patches collected for 5–6 days, 7 days, or 8–10 days after dosing were similar despite large intraand inter-subject variability. However, correlation of patch wear duration to weekly methadone concentration was poor ($r < 0.447$). Even with, identical doses of 60 or 80 mg, there was large within and between-subject variability, with no evidence of a steady state methadone concentration. In fact, with this variability, weekly patch concentrations appeared independent of dose.

Our study cannot be compared to controlled single dose administration studies, as our participants received daily methadone doses. Given the longer detection window possible with sweat monitoring and the relatively long half-life of methadone, it is unlikely that we are only detecting methadone from the day of ingestion. Residual excretion from the previous dose also can occur^{17, 18}, although we showed that % dose excreted each day decreases exponentially³¹. Further controlled administration studies are necessary to evaluate residual excretion of methadone in sweat.

In conclusion, the interpretation of methadone and other drugs in sweat is challenging due to numerous complex factors. Statistical evaluation of sweat patch concentrations demonstrated both intra- and inter-subject variability. Even data with identical dose and patch wear duration demonstrated standard deviations greater than mean values. The extensive variability observed precludes utilization of sweat patches as quantitative biomarkers for therapeutic drug monitoring, or as a basis for predicting the amount of drug exposure. Current research is underway to determine if biological markers for the amount of sweat excreted can function as internal standards to reduce variability of drug excretion. The primary advantage of sweat testing in this population was the ability to monitor illicit drug relapse, rather than attempting to correlate methadone sweat concentrations with methadone dose. However, sweat remains a valuable alternative matrix for qualitatively monitoring drug use history and compliance with methadone medication assisted treatment.

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Figure 1.
Time course of methadone excretion in sweat patches worn for different durations (3–12 days) and following identical daily methadone doses (60, 70 or 80 mg)

Figure 2.
Excretion profiles of weekly patch concentrations (ng/patch) and weekly methadone dose (mg) from 3 representative subjects.

Table 1

Correlation coefficients (r) for sweat patch wear period and methadone concentrations in sweat patches, grouped by duration of patch wear

Patch wear duration (days)	N	r*
Less than 5	46	0.097
5 or 6	55	0.279
7	141	0.252
More than 7	69	0.145
Total (2 – 24)	311	0.129

Table 2

Methadone concentrations in weekly sweat patches (N=49) worn for different wear periods from 13 women receiving 70 mg daily methadone.

Patch Wear Duration (days)	Patches (N)	Mean $\pm$ SD (ng/patch)	Median (ng/patch)	Range (ng/patch)
Less than 5	4	799.8 $\pm$ 326.4	854.8	367.6 – 1121.8
5 – 6	11	2082.2 $\pm$ 1808.3	1933.2	144.7 – 6206.7
7	24	1609.0 $\pm$ 1606.6	1019.4	44.2 – 6266.7
More than 7	10	1992.3 $\pm$ 1113.2	1759.7	776.2 – 4493.0
Total	49	1727.3 $\pm$ 1509.7	1286.3	44.2 – 6266.7

Table 3

Individual and cumulative concentrations (ng/patch) of methadone in hourly (0–12, 12–24 h) and daily (0–24 h) sweat patches after daily methadone dosing. Women (N = 5) participated multiple times during gestation.

Participant N = 13	Daily dose (mg)	0–12 h patch	12–24 h patch	Sum 0–12 h & 12–24 h patches	0–24 h patch
A - 1	30	22.1	18.0	40.1	18.6
A - 2	20	0.0	48.5	48.5	63.1
B - 1	80	0.0	0.0	0.0	17.9
B - 2	90	13.2	11.9	25.0	16.5
C - 1	60	63.6	153.9	217.5	114.4
C - 2	80	36.1	28.9	65.0	155.4
C - 3	95	85.3	66.1	151.4	67.8
C - 4	100	479.1	1870.3	2349.4	610.6
D - 1	90	394.5	382.5	777.0	385.6
D - 2	70	48.9	10.2	59.0	78.0
E - 1	80	62.2	121.8	184.0	327.7
E - 2	90	342.1	66.2	408.3	83.9
E - 3	100	2047.1	2131.2	4178.4	3303.9
Total		3594.2	4909.4	8503.7	5243.4
Mean ± SD		276.5 ± 556.7	377.6 ± 729.3	654.1 ± 1235.0	403.3 ± 889.3
Median		62.2	66.1	151.4	83.9
Range		0.0 – 2047.1	0.0 – 2131.2	0.0 – 4178.4	16.5 – 3303.9
r*		0.424	0.449		0.365

Mean ± SD, median and range are expressed in ng/patch

Correlation coefficient (r) between methadone dose and methadone concentration in sweat patches.