# Elimination of Cotinine from Body Fluids: Implications for Noninvasive Measurement of Tobacco Smoke Exposure

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**Abstract:** Cotinine elimination from plasma, saliva, and urine was studied over 11 days in five subjects (three nonsmokers and two occasional smokers). Half-lives for cotinine averaged 16–19 hours in the different body fluids (range 10 to 27 hours between subjects). There was no tendency for the half-life in saliva to be longer than in plasma or urine. We conclude that choice of body fluid for cotinine assay in smoking studies should depend on practical rather than pharmacokinetic considerations. *(Am J Public Health* 1988; 78:696–698.)

## *Introduction*

Much recent work has pointed to the value of cotinine as a quantitative index of tobacco smoke exposure.[1] As a major metabolite of nicotine it shares with its parent compound the advantage of being specific to tobacco, and its longer half-life (about 20 hours on average) makes sample timing in relation to cigarette smoking less critical. Cotinine concentrations have been used a measure of intake of nicotine in smokers of cigarettes with varying yields[2-4] and as a marker of exposure to other people's smoke in nonsmokers.[5-7] Another important area of application is in validating claims of smoking cessation.[8,9]

Cotinine can be measured in a variety of body fluids, including blood, saliva, urine, breast milk, and cervical mucus. Noninvasive samples of urine and saliva are of particular interest for field studies in such settings as schools, workplaces, and general medical practices. The usefulness of such samples requires a consistent relationship between concentrations in urine and saliva and in blood. We had thought that concentrations in blood, saliva, and urine were very highly correlated and that these body fluids could be used more or less interchangeably.[5,10,11] However, a recent report has suggested that elimination of cotinine from saliva is slower than from blood or urine.[12] Those authors indicated that after cessation of smoking, blood and urine cotinine concentrations declined to nonsmoking levels within three to four days, but saliva concentrations, after decreasing from about 600 ng/ml to 300 ng/ml in three days, showed no further decline for up to one week. Further concern about the extent of applicability of cotinine measurements to other smoking issues, especially estimation of nicotine intake from passive smoking, has arisen from a report that the plasma half-life in nonsmokers may be over twice as long as in smokers (50 vs 18 hours).[13]

Results from these two studies raise important questions about the use and interpretation of cotinine measures. If confirmed, they would force reconsideration of the suitability of different body fluids to estimate blood concentrations of cotinine, and would mean that cotinine concentrations might not provide a reliable guide to the proportional exposure to tobacco smoke from passive and active smoking. The present study was therefore designed to examine further the elimination of cotinine from blood, urine, and saliva. To minimize any possibility that analytical error might influence interpretation of results, specimens were assayed independently by two laboratories with extensive experience in measurement of tobacco alkaloids.

## *Methods*

Subjects were five volunteers from the staff of the Addiction Research Unit. There were three men and two women (mean age 38.0, range 27 to 54). One subject had never smoked, two were ex-cigarette smokers, and two were current smokers of two to three cigars per week (ex-cigarette smokers). All subjects abstained from smoking over the period of the study.

The study design required subjects to develop a high body cotinine level and then to cease nicotine intake while cotinine elimination was followed over an 11-day period. Cotinine levels were generated by ingestion of nicotine capsules. This route of administration was chosen to achieve high cotinine levels without similarly high nicotine levels, which might not be well tolerated by nonsmoking subjects. Extensive first pass metabolism should ensure conversion to cotinine with only small amounts of nicotine reaching the systemic circulation unchanged. Subjects ingested 28mg nicotine base per day (7 × 4mg capsules taken every two hours) over a five-day period in order to achieve cotinine concentrations similar to those from smoking. Dosing with nicotine ceased on a Sunday evening, and sampling commenced on the following morning (Day 0). Each day from Monday to Friday in the first week blood samples were taken at 10am. Saliva and urine samples were gathered at the same time and again at 4pm in the afternoon. In the second week, samples of all fluids were taken on Monday and Friday at 10am, and additional urine and saliva samples were taken on Wednesday at 10am. Specimens were split and assayed for cotinine blindly and independently by two laboratories using gas chromatographic methods.[14,15]

## *Results*

Following the period of nicotine ingestion, mean concentrations of cotinine were 294 ng/ml in plasma, 350 ng/ml in saliva, and 1394 ng/ml in urine, values similar to those found in smokers.[5] Concentrations declined to nonsmoking values in all fluids by Day 4 (< 10 ng/ml in plasma and saliva and < 50 ng/ml in urine). In all subjects the elimination of cotinine over the first four days followed a log-linear course. Half-lives were calculated by linear least squares regression over this period and are shown in Table 1. The results were similar among body fluids and between laboratories. There was no tendency for cotinine in saliva to display a longer half-life than in plasma or urine. The two subjects with the

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**Editor's Note:** See also related briefs, pp 694, 699 and letters, p 718, this issue.

**TABLE 1—Cotinine Half-life (hours) in Plasma, Saliva, and Urine Assessed by two Laboratories**

| | Plasma | | Saliva | | Urine | |
|---|---|---|---|---|---|---|
| Subjects | Lab 1 | Lab 2 | Lab 1 | Lab 2 | Lab 1 | Lab 2 |
| 1 | 15.0 | 15.4 | 16.6 | 13.4 | 16.7 | 17.9 |
| 2 | 15.1 | 14.1 | 15.7 | 14.6 | 14.7 | 15.8 |
| 3 | 14.1 | 14.8 | 13.9 | 9.8 | 13.7 | 16.4 |
| 4 | 21.3 | 19.9 | 22.1 | 18.8 | 23.0 | 26.6 |
| 5 | 17.6 | 16.7 | 18.9 | 15.0 | 17.8 | 17.8 |
| Mean | 16.6 | 16.2 | 17.4 | 14.3 | 17.2 | 18.9 |

NOTE: S1 was a never-smoker; S2 and S3 were ex-cigarette smokers; S4 and S5 were current occasional cigar smokers (ex-cigarette smokers).
T1/2 was calculated by linear regression of log cotinine against time (hours) from Day 0 to Day 4.

longest half-lives (S4 and S5) were both occasional smokers. Figure 1 presents the data from a single subject and illustrates the good agreement between body fluids and between laboratories and the excellent log-linearity of cotinine elimination. The average ratios of cotinine concentration in saliva to plasma were 1.15 and 0.97 for the two laboratories.

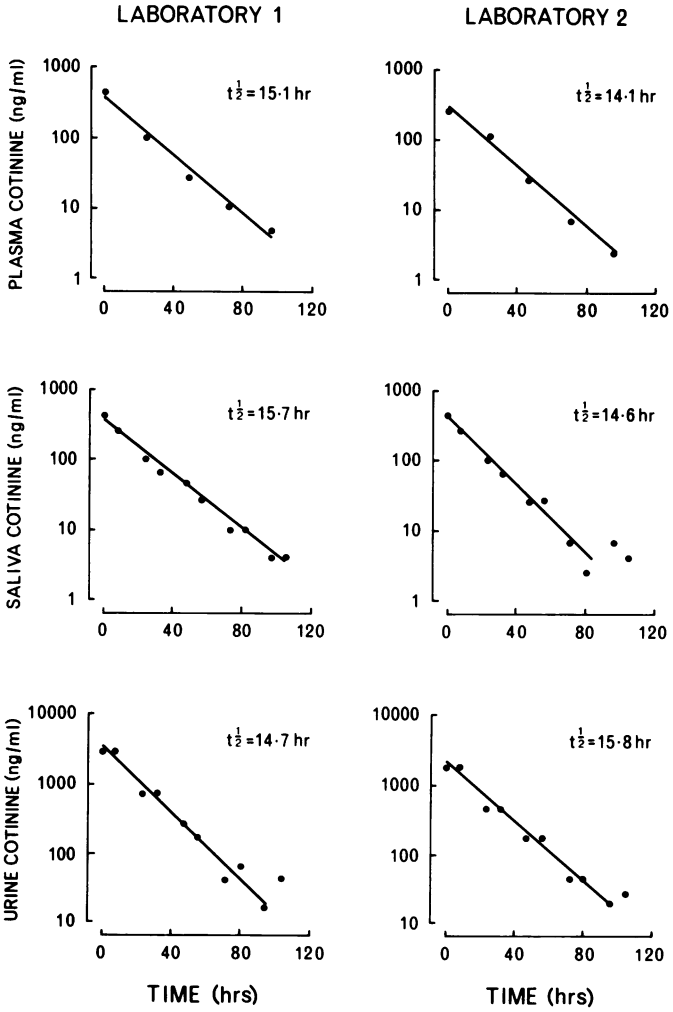


**FIGURE 1—Elimination of Cotinine from Plasma, Saliva, and Urine in a Single Subject (S2) as Assessed by two Laboratories Using Gas Chromatographic Methods**

*Discussion*

In this study cotinine elimination followed a similar time course in each of the body fluids examined. Our results are consistent with earlier work indicating approximate equilibrium between the concentration of cotinine in plasma and saliva, and do not support recent findings of Sepkovic and Haley[12] which showed large differences in the concentrations and rate of elimination of cotinine from plasma and saliva. We are at a loss to explain how they could have found cotinine concentrations in saliva of around 300 ng/ml coinciding with plasma levels close to the detection limits of their method of assay. This discrepancy might reflect the lower specificity of radioimmunoassay methods for saliva assay, although newer immunoassays based on monoclonal antibodies[16] may obviate this problem. There is a clear need for interlaboratory comparisons to validate radioimmunoassays for saliva cotinine.

Kyerematen, *et al,* found a longer plasma half-life in six nonsmokers (mean 13 hours) than in six smokers (mean 10 hours).[17] Benowitz, *et al,* reported mean values of 16 and 20 hours in two samples of cigarette smokers.[18] Our average plasma half-life of 16 hours falls well within this range and also agrees with the figure of 18 hours reported by Sepkovic, *et al,* for smokers.[13] The nonsmokers in our sample had slightly shorter half-lives than the smokers, but the number of subjects was small. However, the discrepancy between our data and the half-life of 50 hours in nonsmokers as reported by Sepkovic, *et al,*[13] deserves some comment. Inspection of the data in the figure presented by Sepkovic, *et al,* indicates a nonsmoker half-life of about 24 hours rather than the figure of 50 hours reported in the text. In addition, these workers studied the plasma half-life over the concentration range 10–1 ng/ml. At these low levels any ongoing inadvertent exposure to other people's smoke would significantly lengthen the observed half-life.

We conclude that cotinine samples from blood, saliva, and urine are equally applicable to the whole range of issues requiring estimates of nicotine exposure from tobacco smoking. After cessation of smoking cotinine concentrations in all body fluids may be expected to decline to nonsmoking levels within four days in the majority of cases, with an upper limit of seven days. Choice of fluid for sampling will depend on practical rather than pharmacokinetic considerations. Marked differences in half-life between smokers and nonsmokers seem unlikely on present evidence, but the precise magnitude of any difference must await larger studies.

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## WHO, UNDP Form Unprecedented Alliance on AIDS

The World Health Organization (WHO) and the United Nations Development Programme (UNDP) have formed an unprecedented alliance to expand the global impact of the struggle against AIDS. The agreement forming the alliance was signed March 29 at the United Nations Headquarters in New York by Dr. Halfdan Mahler, Director-General of WHO and William H. Draper III, Administrator of UNDP.

The alliance, initiated by WHO, is consistent with the UN General Assembly resolution of October 1987, which emphasized the need to have a well-coordinated, multi-sectoral approach by the UN system to the prevention and control of the AIDS pandemic. The alliance combines the strengths of WHO as coordinator of international health policy and scientific and technical matters relating to health with that of UNDP, the leader in the field of socioeconomic development. The alliance was approved in principle by the WHO Executive Board in January and the UNDP Governing Council in February.

Through the alliance with UNDP, the global fight against AIDS will be carried through health ministries to all levels of government, such as ministries of education and information, economic planning, development and finance, justice and the interior by using the extensive UNDP Network of Resident Representatives in developing countries.

The WHO-UNDP alliance has significance because it will:

- Help ensure that AIDS is treated as more than a health problem by involving a wide spectrum of government ministries in designing, implementing and evaluating national programs on AIDS;
- Help include AIDS activities in governments' overall development plans, priorities and resource allocation;
- Coordinate UN system support to national AIDS programs and help governments coordinate all external support to their national AIDS programs; and
- Strengthen support for teams from the WHO Global Program on AIDS based in many countries.