

WHO TobLabNet
Official Method
SOP 03

STANDARD OPERATING PROCEDURE FOR DETERMINATION OF TOBACCO-SPECIFIC NITROSAMINES IN MAINSTREAM CIGARETTE SMOKE UNDER ISO AND INTENSE SMOKING CONDITIONS

Tobacco Free Initiative
Tobacco Laboratory Network (TobLabNet)



**World Health
Organization**



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World Health
Organization

World Health Organization Tobacco Laboratory Network

Standard operating procedure for method

Determination of tobacco-specific nitrosamines in mainstream cigarette smoke under ISO and intense smoking conditions

Method:	Determination of tobacco-specific nitrosamines in mainstream cigarette smoke under ISO and intense smoking conditions
Analytes:	3-(1-Nitrosopyrrolidin-2-yl)pyridine(CAS# 16543-55-8) 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (CAS# 64091-91-4) N-Nitrosoanatabine (CAS# 71267-22-6) N-Nitrosoanabasine (CAS# 37620-20-5)
Matrix:	Tobacco cigarette mainstream smoke particulate matter
Last update:	June 2014



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No machine smoking regimen can represent all human smoking behaviour: machine smoking testing is useful for characterizing cigarette emissions for design and regulatory purposes, but communication of machine measurements to smokers can result in misunderstanding about differences between brands in exposure and risk. Data on smoke emissions from machine measurements may be used as inputs for product hazard assessment, but they are not intended to be nor are they valid as measures of human exposure or risks. Representing differences in machine measurements as differences in exposure or risk is a misuse of testing with WHO TobLabNet standards.



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FOREWORD

This document was prepared by members of the World Health Organization (WHO) Tobacco Laboratory Network (TobLabNet) as an analytical method standard operating procedure (SOP) for measuring tobacco-specific nitrosamines (TSNAs) in mainstream cigarette smoke under International Organization for Standardization (ISO) and intense smoking conditions.

INTRODUCTION

In order to establish comparable measurements for testing tobacco products globally, consensus methods are required for measuring specific contents and emissions of cigarettes. The Conference of the Parties to the WHO Framework Convention on Tobacco Control (FCTC) at its third session in Durban, South Africa, in November 2008, “recalling its decisions FCTC/COP1(15) and FCTC/COP2(14) on the elaboration of guidelines for implementation of Articles 9 (*Regulation of the contents of tobacco products*) and 10 (*Regulation of tobacco product disclosures*) of the WHO FCTC, noting the information contained in the report of the working group to the third session of the Conference of the Parties on the progress of its work ... requested the Convention Secretariat to invite WHO’s Tobacco Free Initiative to ... validate, within five years, the analytical chemical methods for testing and measuring cigarette contents and emissions” (FCTC/COP/3/REC/1).

Using the criteria for prioritization set at its third meeting in Ottawa, Canada, in October 2006, the working group on Articles 9 and 10 identified the following contents for which methods for testing and measurement (analytical chemistry) should be validated as a priority:

- nicotine
- ammonia
- propylene glycol (propane-1,2-diol)
- glycerol (propane-1,2,3-triol)
- triethylene glycol (2,2-ethylenedioxybis(ethanol)).

Measurement of these contents will require validation of three methods: one for nicotine, one for ammonia and one for humectants.

Using the criteria for prioritization set at the meeting in Ottawa mentioned above, the working group identified the following emissions in mainstream smoke for which methods for testing and measurement (analytical chemistry) should be validated as a priority:

- 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)
- N-nitrosornicotine (NNN)
- acetaldehyde
- acrylaldehyde (acrolein)
- benzene
- benzo[a]pyrene
- 1,3-butadiene

- carbon monoxide
- formaldehyde

Measurement of these emissions with the two smoking regimens described below will require validation of five methods: one for tobacco-specific nitrosamines (NNK and NNN), one for benzo[a]pyrene, one for aldehydes (acetaldehyde, acrolein and formaldehyde), one for volatile organic compounds (benzene, 1,3-butadiene) and one for carbon monoxide.

The table below sets out the two smoking regimens for validation of the test methods referred to above.

Smoking regimen	Puff volume (mL)	Puff frequency	Filter ventilation holes
ISO regimen: ISO 3308; <i>Routine analytical cigarette smoking machine—definitions and standard conditions</i>	35	Once every 60 s	No modifications
Intense regimen: Same as ISO 3308, but modified as indicated	55	Once every 30 s	All ventilation holes must be blocked 100% as described in WHO TobLabNet SOP 01.

This SOP was prepared to describe the procedure for the determination of TSNAs in mainstream cigarette smoke under ISO and intense smoking conditions.

1 SCOPE

1.1 This method is suitable for quantitative determination of the following four TSNAs in mainstream cigarette smoke: 3-(1-nitrosopyrrolidin-2-yl)pyridine (NNN), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), *N*-nitrosoanatabine (NAT) and *N*-nitrosoanabasine (NAB) by combined high-performance liquid chromatography-tandem mass spectrometry (HPLC–MS–MS).

Note: The Conference of the Parties recommended that only NNN and NNK be measured. Information on the analysis of NAT and NAB is included for laboratories that choose to conduct those measurements.

1.2 NNN and NNK are potent carcinogens; NAB is a weaker carcinogen, while NAT is not carcinogenic. NNN and NNK are not originally present in tobacco leaves but are formed from the nitrosation of nicotine during tobacco curing and storage; NAB is formed from nitrosation of anabasine and NAT from nitrosation of anatabine. After absorption into the body, NNN and NNK can be hydroxylated to compounds that form adducts with haemoglobin or DNA.

2 REFERENCES

2.1 ISO 3402: *Tobacco and tobacco products—Atmosphere for conditioning and testing.*



- 2.2** ISO 4387: Cigarettes—Determination of total and nicotine-free dry particulate matter using a routine analytical smoking machine.
- 2.3** World Health Organization. Standard operating procedure for intense smoking of cigarettes. Geneva, Tobacco Laboratory Network (WHO TobLabNet SOP 01).
- 2.4** ISO 3308: Routine analytical cigarette-smoking machine—Definitions and standard conditions.
- 2.5** ISO 8243: Cigarettes—Sampling
- 2.6** United Nations Office on Drugs and Crime. Guidelines on representative drug sampling. Vienna, Laboratory and Scientific Section, 2009 (http://www.unodc.org/documents/scientific/Drug_Sampling.pdf).
- 2.7** World Health Organization. Standard operating procedure for validation of analytical methods of tobacco product contents and emissions. Geneva, Tobacco Laboratory Network (WHO TobLabNet SOP 02).
- 2.8** World Health Organization. Method validation report of World Health Organization TobLabNet official method: Determination of tobacco-specific nitrosamines in mainstream cigarette smoke under ISO and intense smoking conditions. Geneva, Tobacco Laboratory Network, forthcoming.
- 2.9** ISO 5725-1. Accuracy (trueness and precision) of measurement methods and results—Part 1: General principles and definitions.
- 2.10** ISO 5725-2. Accuracy (trueness and precision) of measurement methods and results—Part 2: Basic method for the determination of repeatability and reproducibility of a standard measurement method.
- 3 TERMS AND DEFINITIONS**
 - 3.1** TPM: total particulate matter
 - 3.2** TSNAs: tobacco-specific nitrosamines
 - 3.3** NNN:3-(1-nitrosopyrrolidin-2-yl)pyridine
 - 3.4** NNK: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
 - 3.5** NAT:N-nitrosoanatabine

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