

GSE → WST [in Trans F under 3169.REP]

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Biomonitoring nicotine uptake:

The concentrations of nicotine (NIC), cotinine (COT), and *trans*-3'-hydroxycotinine (THOC) were determined by gas chromatography in urine samples collected during as well as after the exposure period for approx. 1 day (Table 1). The molar amounts of excreted NIC, COT, and THOC were calculated (Table 2). One should take into consideration that the concentrations of NIC and COT might be overestimated due to the fact that under gaschromatographic conditions the metabolites nicotine-N'-oxide and cotinine-N'-oxide decompose thermically to some extent forming among other compounds also some NIC and COT, respectively.

A linear increase of the excreted amounts of NIC, COT, and THOC with increasing concentrations of nicotine and TPM but not of CO in the FSS and CSS smoke was observed (Figure 1 to 3). In addition, a linear relation was found between the total amount of NIC, COT, and THOC excreted and the nicotine theoretically inhaled, calculated from the respiratory minute volume according to Guyton (1947) and the nicotine concentrations in the different smoke types determined at the respective days of urine collections (Table 3 and Figure 4). This indicates that the determination of the urinary excretion of NIC, COT, and THOC can be considered as a good biomonitor for inhaled nicotine, at least for SS concentrations in the range used in this study.

The total amount of NIC, COT, and THOC accounts for between 20 % in the lowest CSS-group and 34 % in the highest FSS-group relative to the amount of nicotine theoretically inhaled (Table 2). There is a tendency to a higher recovery with amounts concentrations of nicotine inhaled (Figure 5), however these differences are considered to be not significant. The recovery is somewhat higher but in the same range as the recovery found for NIC, COT, and THOC in

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24 hours urine following i.v. administration of S-nicotine to non-induced male rats (19 %) and Aroclor-induced male rats (14%) (INBIFO study P 0500/3146).

In each SS group, except in the lowest CSS group, the amounts of excreted NIC and COT were almost similar whereas a significantly lower amount of THOC was excreted. This is in accordance with results found in a previous SS-inhalation study (INBIFO study P 0500/3149). In the above mentioned nicotine metabolism study (INBIFO study P 0500/3146) the ratios NIC:COT:THOC were found to be different: 1.00:0.44:0.32 for the noninduced and 1.00:0.30:1.33 for the Aroclor-induced male rat. The different profiles found in the SS-inhalation studie might indicate that nicotine inhalation from SS smoke might cause a different metabolic pathway than intravenous administration of nicotine or that SS components might induce the metabolism from NIC to COT but not - as Aroclor does - the further metabolism of COT.

As in the previous SS-inhalation study (INBIFO study P 0500/3149), small amounts of NIC, COT, and THOC are also found in the urine of sham-exposed and cage-control rats (Table 1). Since in these urine samples predominantly the nicotine metabolites COT and THOC are found, contamination of the samples with environmental nicotine (either during sample collection or sample preparation) seems to be unlikely. More likely seems the possibility that small amounts of nicotine were taken up also by these rats, however, a straightforward explanation is not available.

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Figure 1: URINARY EXCRETION OF NICOTINE, COTININE, AND *trans*-
3'-HYDROXYCOTININE AS A FUNCTION OF TPM IN SMOKE

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Figure 2: URINARY EXCRETION OF NICOTINE, COTININE, AND *trans*-3'-
HYDROXYCOTININE AS A FUNCTION OF NICOTINE IN SMOKE

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Figure 3: URINARY EXCRETION OF NICOTINE, COTININE, AND *trans*-3'-
HYDROXYCOTININE AS A FUNCTION OF CO IN SMOKE

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Figure 4: URINARY EXCRETION OF NICOTINE, COTININE, AND *trans*-3'-HYDROXYCOTININE AS A FUNCTION OF INHALED NICOTINE

Remarks: Inhaled nicotine was theoretically calculated according to Guyton (1947) by using body weight and nicotine in smoke on the exposure day when urine collection was started.

Calculation of the regression line was performed by using the single values (n=5 for each point)

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Figure 5: PERCENTAGE OF RECOVERY OF NICOTINE, COTININE, AND *trans*-3'-HYDROXYCOTININE IN URINE AS A FUNCTION OF INHALED NICOTINE

Remarks: Inhaled nicotine was theoretically calculated according to Guyton (1947) by using body weight and nicotine in smoke on the exposure day when urine collection was started.

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