

German Human Bitumen Study



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Irritative and Genotoxic Effects of Vapours and Aerosols of Bitumen

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Health hazards of vapours and aerosols of bitumen

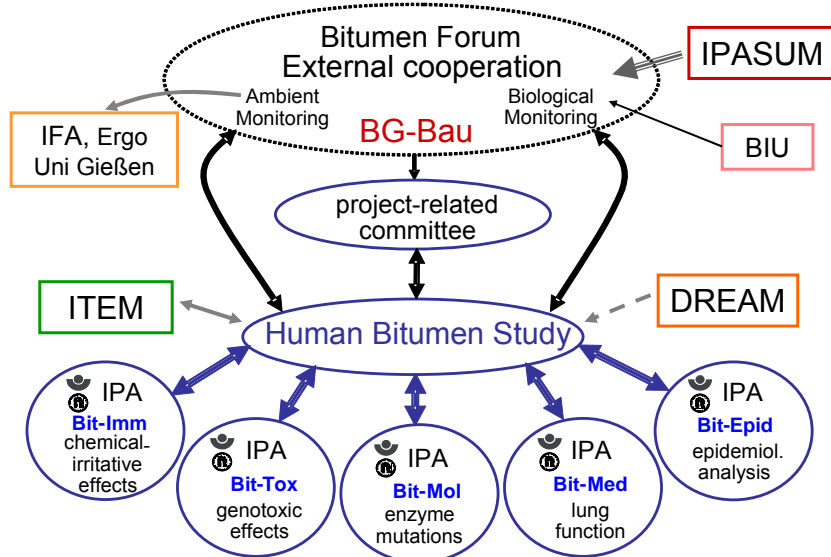


- Of specific concern is the potential **carcinogenicity of the inhalation of fumes of bitumen**.
 - ⇒ IARC classification 1985/87: **possible human carcinogen**
 - ⇒ MAK Germany 1977: **suspected carcinogen**
- In 2001, the **German Committee for Hazardous Substances (AGS) lowered the threshold limit value** for vapours and aerosols of bitumen **to 10 mg/m³**; for mastic asphalt workers the exposure limit value was **temporarily** deferred.
- In 2005 all technical based threshold limit values have been suspended.
- A mortality analysis of non-malignant diseases revealed the highest mortality from respiratory diseases in pavers and mastic asphalt workers (Randem, 2003).
- **Data on irritative/genotoxic effects of bitumen** under current **exposure conditions** in humans **are limited**.

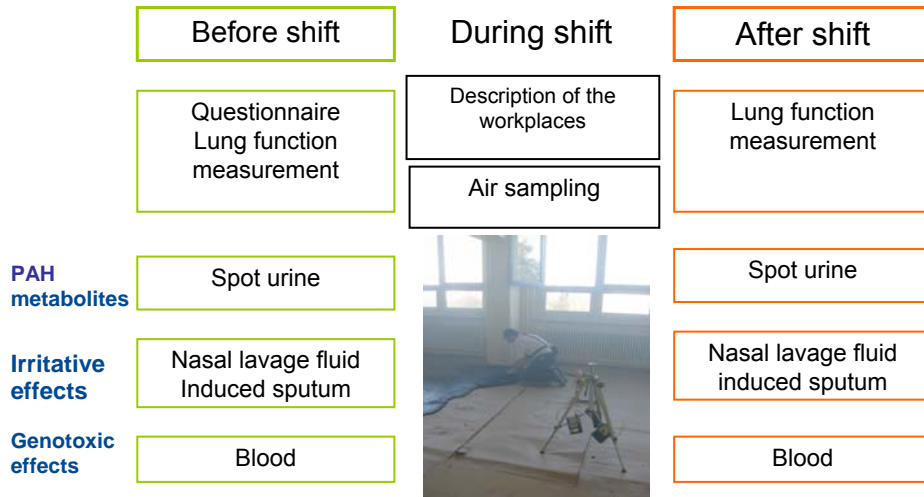
Assignment of the German Bitumen Forum 2000

➔ Investigation of irritative and genotoxic effects of vapours and aerosols of bitumen in particular for mastic asphalt

German Human Bitumen Study

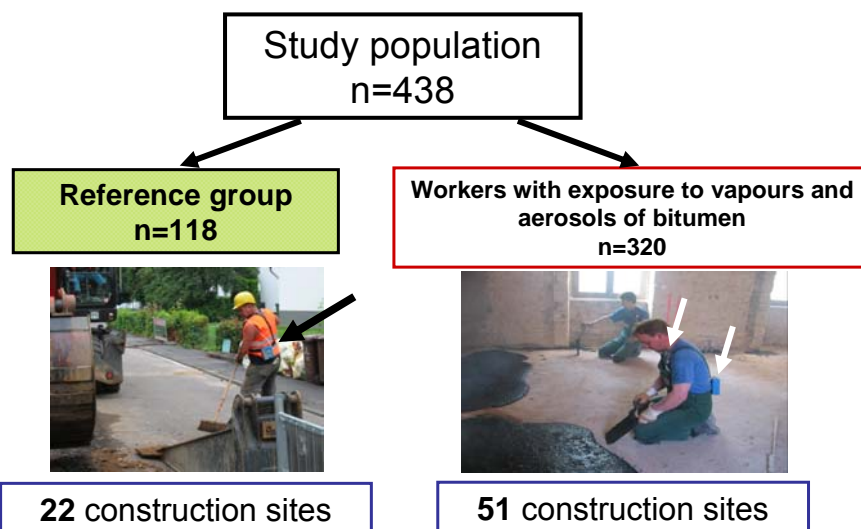


Cross-shift Design



Study group

Examination of 500 workers



Characteristics of the study population

Attribute	References	Exposed (total)
	n=118	n=320
Exposure to vapours and aerosols of bitumen* (mg/m ³) (median; IQR)	0.17 (0.07-0.3) (n=69)	3.46 (1.8-5.9)
Age (years) (median; range)	41 (18-64)	41 (17-63)
Current smoking n (%)	61 (51.7%)	199 (62.2%)
German nationality n (%)	96 (81.4%)	218 (68.3%)

* Mineral oil standard

External exposure

⇒ During the whole shift

- personal measurements
 - vapours and aerosols
- stationary measurements
 - vapours/aerosols
 - 16 EPA-PAH



External exposure

Bitumen is a complex mixture of organic compounds

→ Lack of a specific method to measure bitumen exposure

Sampling and analysis are different

U.S.: 37-mm cassette < inhalable fraction

Germany: GGP sampler inhalable fraction

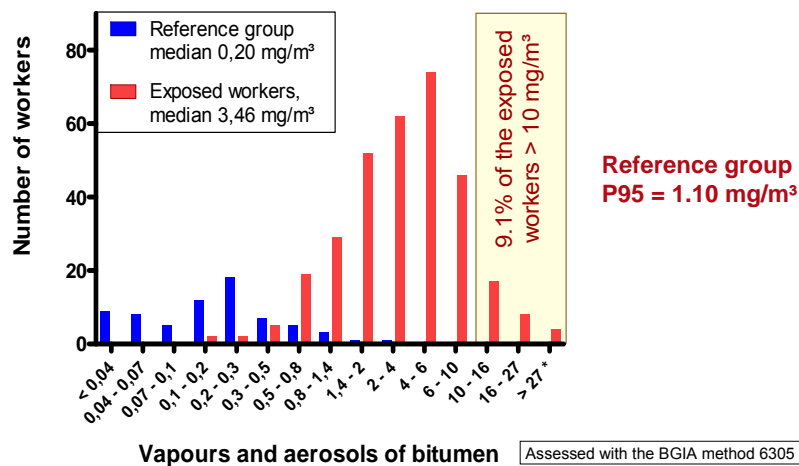
U.S.: NIOSH method 4502 Benzene-soluble matter in aerosols

Germany: BGIA method 6305; C-H stretches in vapours and aerosols

U.S.: benzene-soluble matter

Germany: C-H stretches, mineral-oil standard until 2008

Background “bitumen” exposure up to 1 mg/m³ according to BGIA method 6305



*Numbers are rounded.

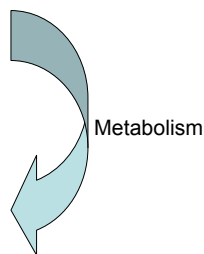
Summary I

- **Lack of a specific method to measure bitumen exposure**
- Significant disparity in the sampling and analytical methods between various countries
- In Germany: GGP sampler; inhalable fraction; BGIA method 6305: C-H stretches in vapours and aerosols
- **Background exposure up to 1.1 mg/m³ has to be considered**
- Frequent changes of the construction sites and of the workplace conditions impair the assessment of lifetime exposure
- Reduction of the exposure to vapours and aerosols of bitumen by lowering the application temperature
- **A single shift measurement of bitumen is not sufficient to serve as a proxy for an average or lifetime exposure.**

Biological Monitoring



Bitumen exposure

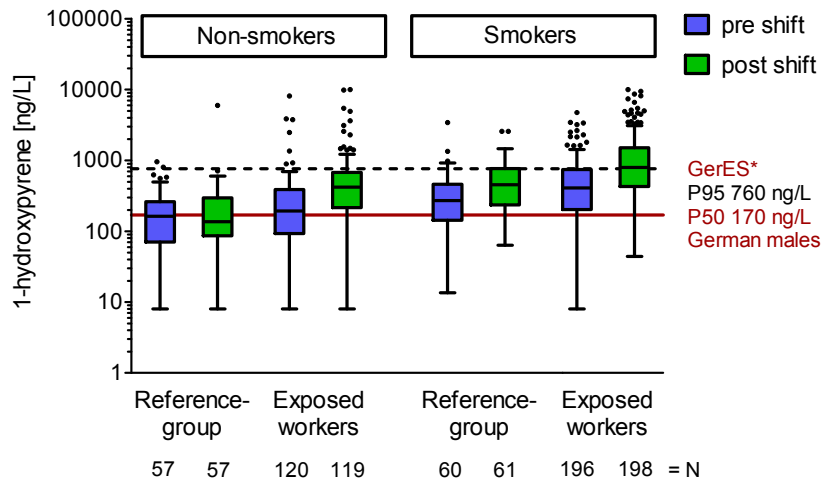


Urinary metabolites

Urinary PAH metabolites

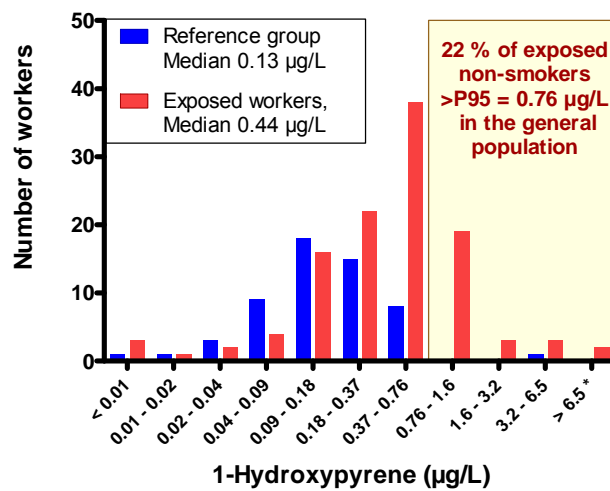
- **1-Hydroxypyrene (1-OHP)**
 - **Di-Hydroxypyrene**
 - **1-Naphthol**
 - **2-Naphthol**
 - **1-OH-Phenanthrene**
 - **2-OH-Phenanthrene**
 - **3-OH-Phenanthrene**
 - **4-OH-Phenanthrene**
 - **9-OH-Phenanthrene**
 - **Phenanthrene tetrol**
 - **1,2-Phen-Diol**
 - **9,10-Phen-Diol**
- } Σ OHPHE

Smoking and bitumen exposure contribute to 1-OHP



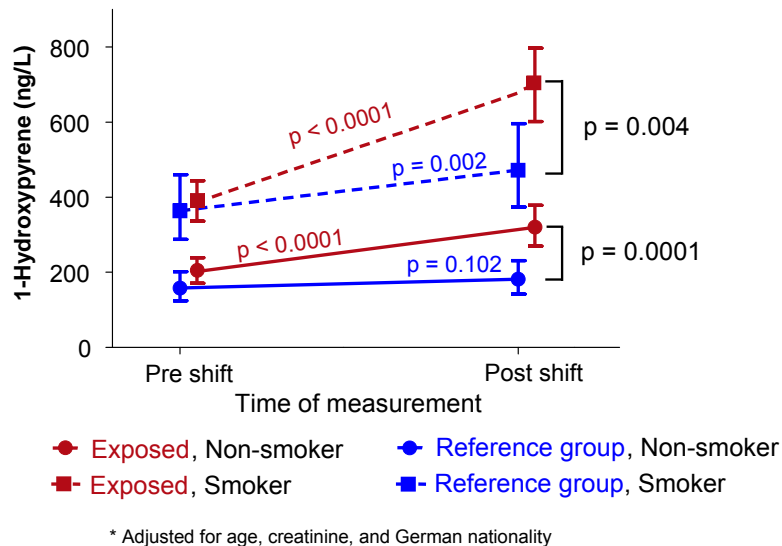
* GerES: German Environmental Survey (1998)

1-Hydroxypyrene concentrations post shift in exposed and non-exposed non-smokers



* Numbers are rounded .

Mixed linear model for 1-hydroxypyrene (1-OHP)*



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Conclusions on PAH metabolite analysis in the Human Bitumen study

- Bitumen exposure during shift was associated with an **increase of certain PAH metabolites** (1-OHP and Σ OHPHE) in urine.
- 22% of bitumen-exposed non-smokers had 1-OHP-concentrations above the 95th percentile in German men.
- The concentrations of the PAH metabolites were **much lower in bitumen-exposed workers** than in “typical” PAH settings such as coke-oven works.
- Smoking is an important predictor of the metabolite concentrations in urine.

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Lung function

height
weight } Calculation of the BMI index

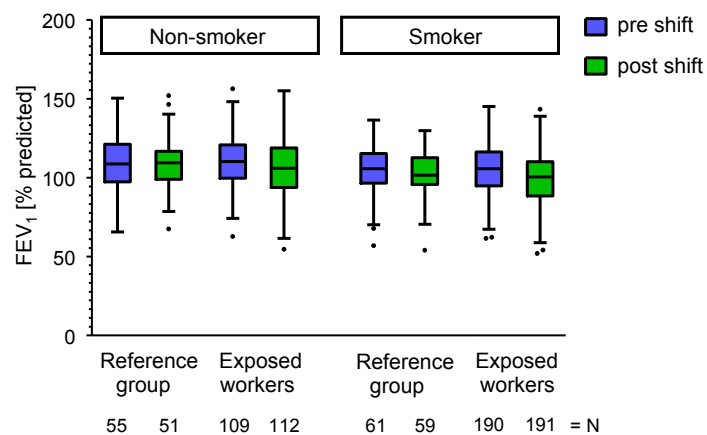
Key-variables:

- FVC [% predicted]
- FEV₁ [% predicted]
- FEV₁ % /FVC [%]
- MEF 50 % [predicted]
- Maximum vital capacity [L] (VC_{max})



According to the ATS guidelines

Lung function: FEV₁ % predicted



Lung function measurements (Summary)

- There are unremarkable lung function results (generally better than the predicted values; “healthy workers”).
- Only weak influence of the bitumen exposure during the shift can be observed.
- Overall, only weak effects on lung function parameters are detectable.

Upper airways NALF analysis (Summary)

- No significant differences between bitumen-exposed workers and the reference group could be observed on the upper airways using NALF analysis.
- No significant shift-effects could be observed on the upper airways using NALF analysis.



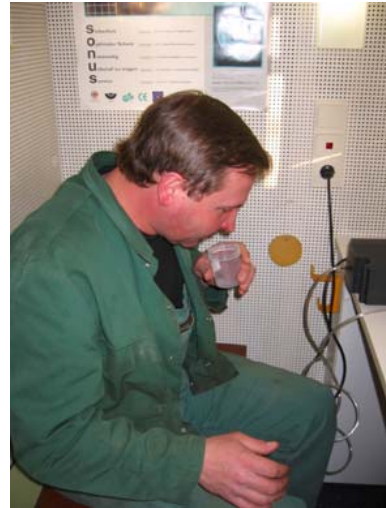
Irritative effects at the lower airways -Induced sputum-

→ Cellular profile

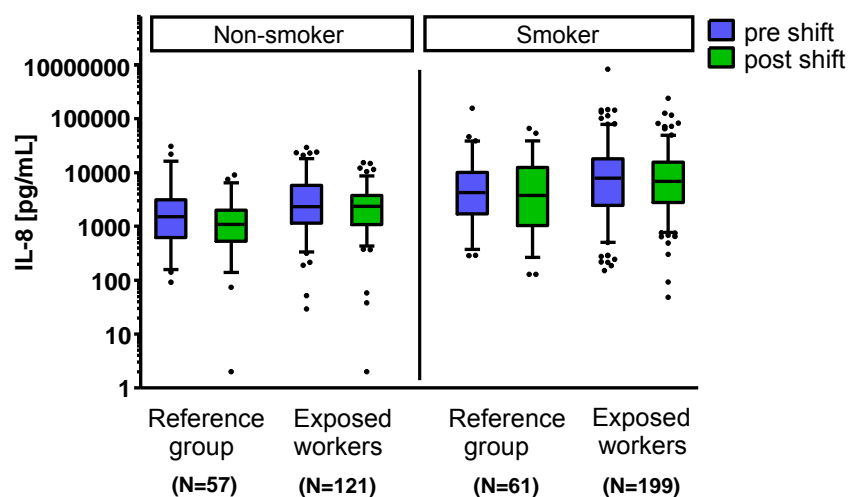
- Total cell count
- Macrophages
- Neutrophiles
- Lymphocytes
- Eosinophiles
- Epithelial cells

→ Soluble (inflammatory) Mediators

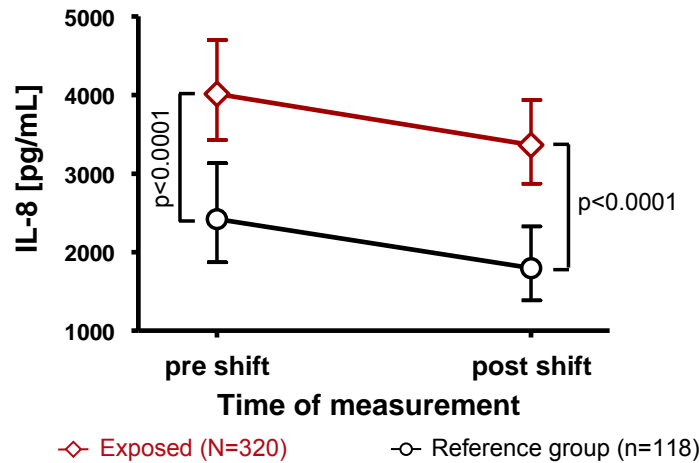
- IL-5 [pg/ml]
- IL-6 [pg/ml]
- **IL-8 [pg/ml]**
- NO Derivates (Nitrat/Nitrit) [μ M]
- IL-1 β [pg/ml]
- TNF- α [pg/ml]
- LTB $_4$ [pg/ml]
- Protein content [μ g/ml]
- MMP-9 [ng/ml]



Sputum: IL-8 concentrations



Induced sputum: IL-8 concentrations*



*Adjusted for smoking and other factors

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Conclusion from biomarkers of inflammation

- ✓ Smoking was confirmed as factor affecting inflammatory marker concentrations in induced sputum samples.
- ✓ Inflammatory sputum markers were **higher before and after shift** in bitumen-exposed workers. This may indicate **effects due to repeated exposure**.
- ✓ **No dose-dependent association** with bitumen exposure could be observed. A single shift measurement of bitumen is not sufficient to serve as proxy for an average or lifetime exposure.

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Genotoxic risk assessment in bitumen exposed workers:

- 8-OxodGuo (8-oxo-7,8-dihydro-2'-deoxyguanosin) **adducts** in white blood cells (biomarker of oxidative DNA damage)
- *anti*-BPDE ((+)-*anti*-Benzo[*a*]pyren-7,8-diol-9,10-epoxid)-DNA adducts in white blood cells (biomarker of exposure to B[*a*]P)
- DNA single and double **strand breaks** and alkali-labile sites in lymphocytes (alkaline version of Comet assay)
- Chromosomal breaks and losses (**micronucleus assay**)

Genotoxic effects I

- ✓ The genotoxic effects were examined **in the blood**.
- ✓ Increased **8-oxodGuo-adduct rates** and **DNA-strand break-frequencies** were detected in the group of bitumen-exposed workers pre and post shift: indication for (sub)chronic effects.
- ✓ A **dose-response-relationship** for bitumen-exposure during a shift could **not be found**.
- ✓ In bitumen-exposed workers **specific DNA adducts** of PAH-exposure (*anti*-BPDE) **were not increased**.

- ✓ The **micronucleus assay** detects chromosomal breaks and -losses *in vivo*. In our study a mutagenic potential of vapours and aerosols of bitumen was not detected.
- ✓ A dose-response relationship can also not derived between bitumen exposure and the micronucleus frequencies.
- ✓ The **age** is detectable as **the most prominent influencing factor**. This is known from the literature and confirms the plausibility of the test results.

Conclusions from the Human Bitumen Study

- ✓ In the **lower airways inflammatory** effects could be detected in the **bitumen-exposed group**.
- ✓ There was **no dose-response relation** for all measured effect markers with bitumen exposure during a single shift.
- ✓ The cross-shift design revealed **increased levels of inflammatory** (pre-clinical?) **markers** already **before shift**. This may indicate effects due to repeated exposure.
- ✓ A single shift measurement of exposure is not sufficient to assess long-term exposure.
- ✓ Assessment of lifetime exposure is impaired by **frequent changes of construction sites**. Workers are not aware of accidental higher PAH exposure ("Schwelm Group").

Many thanks!

- ❖ To all participants of the study
- ❖ To the team of the Human Bitumen Study

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**Thanks for your
attention!!**