GENOTOXIC EFFECTS IN WORKERS EXPOSED TO FUMES OF BITUMEN. COMPARISSON WITH AMBIENT AND BIOLOGICAL MONITORING.

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INTRODUCTION

BACKGROUND

- Bitumen is a complex mixture of hydrocarbons consisting of both aliphatic and aromatic compounds, e.g. polycyclic aromatic hydrocarbons (PAH).
- There is inadequate evidence of carcinogenicity of bitumen in humans. Previous studies cannot be interpreted due to major qualitative or quantitative limitations.
- Overall, bitumen is labelled as „high priority substance" for future evaluation by the International Agency for Research on Cancer.

OBJECTIVE

- To determine genotoxic properties of exposure to fumes of bitumen in humans.
- To generate dose-response relationship which can help to establish health-based threshold limit values for exposed workers.

METHODS

STUDY DESIGN

- Cross-sectional and cross-shift study design.

STUDY SUBJECTS

- 202 bitumen exposed-mastic asphalt workers and 55 construction workers without exposure to bitumen were examined (Table 1).

Table 1: Characteristics of the study groups

	Reference group $n = 55$	Bitumen-exposed workers $n = 202$
Age (years; median, range)	37 (19-61)	40 (17-63)
Current smoking (*n*, %)	23 (41.8)	132 (65.7)
German nationality (*n*, %)	48 (87.3)	136 (67.7)
Duration of exposure in the current company (years; median, interquartile range)	6.5 (3-10)	8 (3-14)
Exposure to bitumen fumes and aerosols (mg/m³; median, interquartile range)	- -	3.7 (1.7-7.1)

ANALYTICAL PARAMETERS

Exposure was assessed using urinary 1-hydroxypyrene (1-OHP) and the sum of 1-,2+9-,3-,4-hydroxyphenanthrene (OHPH). Genotoxic effects in white blood cells were determined with non-specific DNA adduct levels of 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodGuo) and the formation of DNA strand breaks and alkali-labile sites.

STATISTICAL MODEL

- Linear mixed model with log-transformed study variables and control of confounders (SAS Software).
- Implemented in the model are independent fixed factors (time of measurements, smoking status, ethnicity) and a random factor (participants).
- Age is included in the model as a continuous independent variable.
- Results presented are means adjusted for the set of potential confounders and F-tests (*P*-values) for the exposure effect.

RESULTS

The urinary concentrations of 1-OHP and OHPH of exposed and non-exposed workers were similar before shift ($P = 0.68$, and $P = 0.21$, respectively) but different after shift ($P = 0.003$, and $P = 0.002$, respectively, Fig. 1). Concentrations of fumes of bitumen were moderately associated with 1-OHP and OHPhe after work shift ($r_s = 0.25$, $P < 0.001$ and $r_s = 0.36$, $P < 0.001$, respectively, Table 2). Significantly more 8-oxodGuo adducts and DNA strand breaks were found in bitumen-exposed workers pre- and post-shift compared with the reference group (Fig. 1). Significantly increased 8-oxodGuo adduct levels were observed post shift in both groups ($P < 0.0001$; Fig. 1). Paradoxically, decreased DNA strand break frequencies were observed after shift in both groups ($P < 0.05$; Fig. 1). No dose-dependent association was observed between exposure to fumes of bitumen and genotoxic effects (Table 2). However, post shift values in DNA strand break frequency were associated with 1-OHP ($r_s = 0.19$, $P = 0.01$; Table 2).

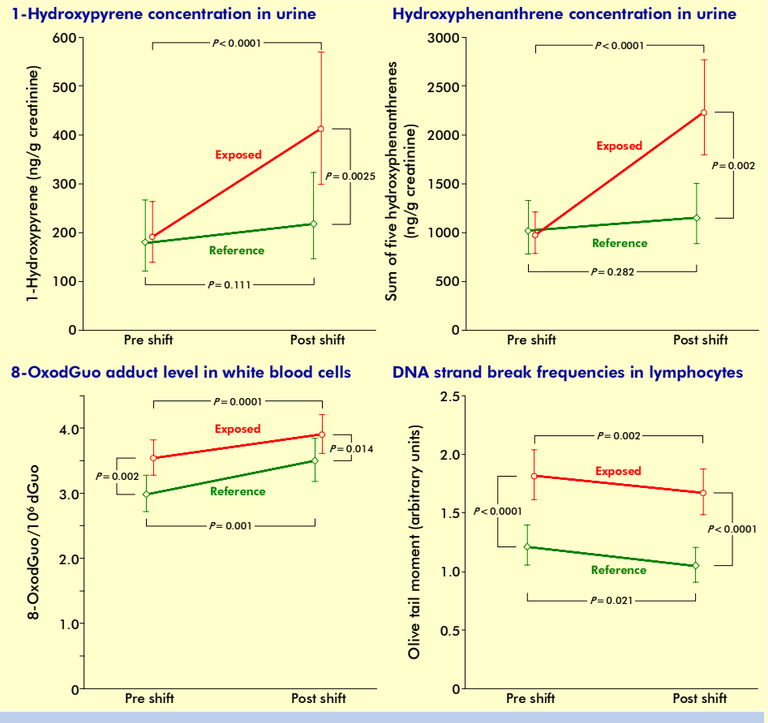

Fig. 1: Biomarker levels before and after shift presented as adjusted geometric means and 95% confidence intervals.

Table 2: Spearman rank correlations between exposure to fumes of bitumen, urinary metabolites, 8-oxodGuo and Olive tail moment

Parameter	Independent variables	Preshift			Postshift			Shift difference[4]		
		n	r_s	*P*	*n*	r_s	*P*	*n*	r_s	*P*
Exposure to fumes of bitumen (mg/m³)	1-OHP [ng/L]				199	0.26	<0.001			
	1-OHP [ng/g crea]				199	0.25	<0.001			
	OHPhe [ng/L]				199	0.36	<0.001			
	OHPhe [ng/g crea]				199	0.36	<0.001			
	8-OxodGuo/10⁶dG				201	-0.02	0.76			
	Olive tail moment (median)				202	0.00	0.97			
1-OHP (ng/L)	Sum of five OHPHs [ng/L]	198	0.73	<0.001	199	0.76	<0.001	195	0.73	<0.001
	8-OxodGuo/10⁶dG	196	-0.01	0.94	198	0.05	0.46	192	0.01	0.90
	Olive tail moment (median)	197	-0.05	0.52	199	0.17	0.01	194	0.22	<0.001
1-OHP (ng/g crea)	Sum of five OHPHs [ng/g crea]	198	0.61	<0.001	199	0.66	<0.001	195	0.61	<0.001
	8-OxodGuo/10⁶dG	196	-0.02	0.83	198	0.02	0.82	192	0.03	0.65
	Olive tail moment (median)	197	-0.07	0.30	199	0.19	0.01	194	0.15	0.03
Sum of five OHPhes (ng/L)	8-OxodGuo/10⁶dG	196	0.05	0.50	198	0.00	0.97	192	0.02	0.81
	Olive tail moment (median)	197	-0.02	0.74	199	0.01	0.84	194	0.12	0.09
Sum of five OHPhes (ng/g crea)	8-OxodGuo/10⁶dG	196	0.03	0.70	198	-0.04	0.58	192	0.07	0.33
	Olive tail moment (median)	197	-0.06	0.39	199	0.01	0.92	194	0.03	0.72
8-OxodGuo/10⁶dG	Olive tail moment (median)	199	-0.19	0.01	201	0.08	0.28	198	0.02	0.73

CONCLUSIONS

- Exposure to fumes of bitumen results in excretion of 1-OHP and five isomers of OHPH in urine after the shift.
- The excretion of urine metabolites was dependent on bitumen fume concentrations. Therefore, 1-OHP and sum of OHPH are suitable biomarkers to assess exposure to fumes of bitumen.
- Exposed workers had higher levels of oxidative DNA damage (8-oxo-dGuo) and higher frequencies of DNA strand breaks in both pre- and postshift blood samples compared to non-exposed individuals. Consequently these workers show increased biomarkers of genotoxicity.
- Increases in oxidative DNA damage during the shift were of statistical significance but did not depend on external exposure. Therefore, 8-oxo-dGuo is capable to assess oxidative DNA damage but is not specific of exposure to fumes of bitumen.
- Decreases of DNA strand breaks (significant) were observed after shift in both study groups. A good correlation was found between DNA strand break frequencies and 1-OHP concentrations after shift.
- Due to only weak association between 1-OHP and DNA strand breaks the reasons for increased DNA damage in workers exposed to fumes of bitumen remains unclear.

ACKNOWLEDGEMENTS

The authors wish to thank the different members of the Statutory Accident Insurances of the Federal Republic of Germany for their organizational and financial support during the field studies.