SIDE EFFECTS OF METHYL BROMIDE ON PHARMACEUTICALS AFTER FUMIGATION IN CONTAINERS?

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1. Introduction

Container with any goods where wood or wooden parts are used for stowing the goods (pallets) and to fix them in the container (ply wood) have to be treated with either methyl bromide or heat to prevent the importation of quarantine insects which may be hidden in the wooden articles according to the requirements of ISPM 15. ISPM 15 is the international standard for these kinds of treatments. In practice heat cannot always be used instead of methyl bromide because of logistic and other reasons. Due to these requirements many goods like mattresses, bags, shoes, toys for children and various other items are exposed to methyl bromide and release the gas slowly after the treatment. The regular dose is 80 g methyl bromide per m³ which are applied for several hours. The end-user of these non intentionally fumigated items is therefore exposed to the risk of inhaling desorbed methyl bromide. In a study of the Netherlands this aspect was intensely investigated and showed that indeed methyl bromide was desorbed from fumigated items in considerable amounts over a long time of several months. The senate of Hamburg received this Dutch information and decided in the interest of consumer protection to investigate as soon as possible the hazard which may derive from fumigated pharmaceuticals. The presented data are derived from this study of Hamburg.

2. Material and Methods

The chemical structure of alkenes, alcohols, amines, carbonic acids and thioles was suspected for a possible reaction with methyl bromide. Therefore, the pharmaceuticals in Table 1 were selected. Beside of the single active ingredients also a solution mixture with procaine and chloric acid was selected.

To simulate a high risk, the substances were exposed in open glass flasks to methyl bromide. For the simulation of realistic transport conditions metformin was additionally packed in two plastic bags and the procaine containing injection solution was exposed in the as original as injection flask closed with a septum.

The fumigation was carried out in desiccators at 25°C and 60% r.h. with 80 g methyl bromide per m³ over 24 hours.
To simulate the efficacy of desorbing methyl bromide in a container after the aeration, metformin was exposed for three weeks with 0.2 g per m³.
The contents of the original active ingredient, bromide and possible reaction products was investigated immediately after the treatment by use of HPLC/UV/MS and GC/ECD. The details of these determinations are described in Langfermann et al. (in preparation).

3. Results

The results are described in the Tables and Figures. Concerning the procaine containing selection solution (Figures 1 and 2), impurities with the mass number of 323 increased from 0.06% in untreated to 0.1% in the treated sample.
Altogether there were only little differences between the treated and the untreated sample.

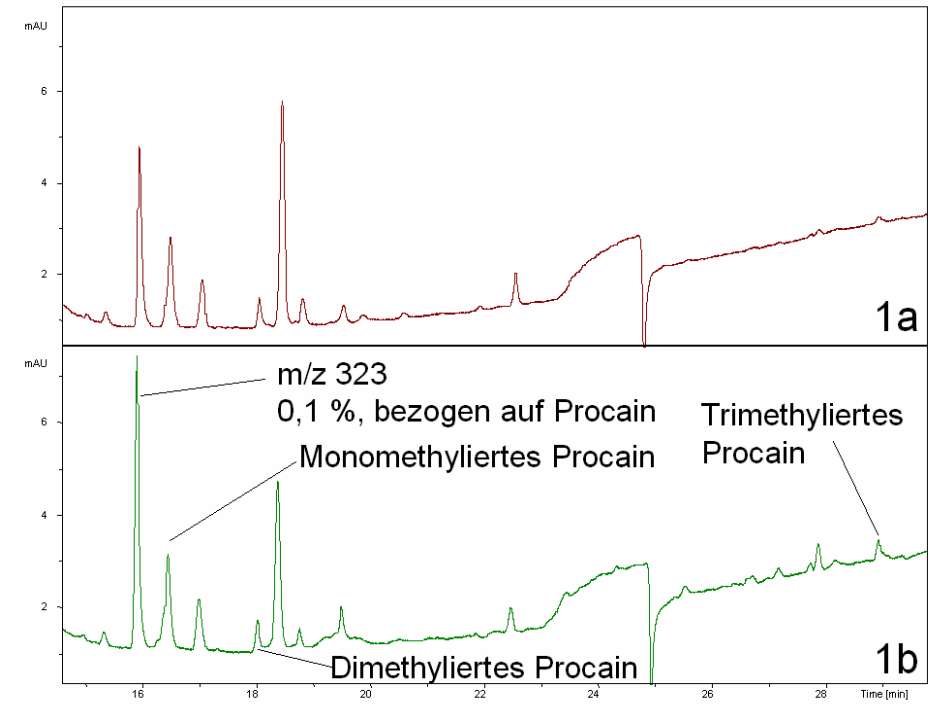

Figure 1 HPLC/UV-MS-Analysis of the procaine containing mixture, Method 2 (1a: reference sample for comparison; 1b: sample after exposure to methyl bromide)

In phenacetine an increase of bromide content was found. From the Figures it can be deducted that about 0.04% reacted with methyl bromide. Possibly it is methylated phenacetine. Again the changes were not pronounced.
The clinical effects of uptake of inorganic bromide are well known from experiments with animals. Bromide has been used as sedative with a daily dose of 100 mg/kg bw. Bromide is quickly sorbed in the stomach. The toxicological effect of bromide relies on the exchange of the bromide and chloride ion. The acute oral toxicity is low. A longer concentrations in the

plasma of 100 mg/l showed symptoms of bromine poisoning. The lower limit of effects is in the range of 9 mg bromide per kg bw and day. The no observed effect level (NOEL) is about 4 mg bromide/kg bw and day. To estimate the amount which can be incorporated during a whole life the European agency for the evaluation of medicinal products (EMEA, 1997) fixed a uncertain factor of 10 and the corresponding ADI value of 0.4 mg bw and day.

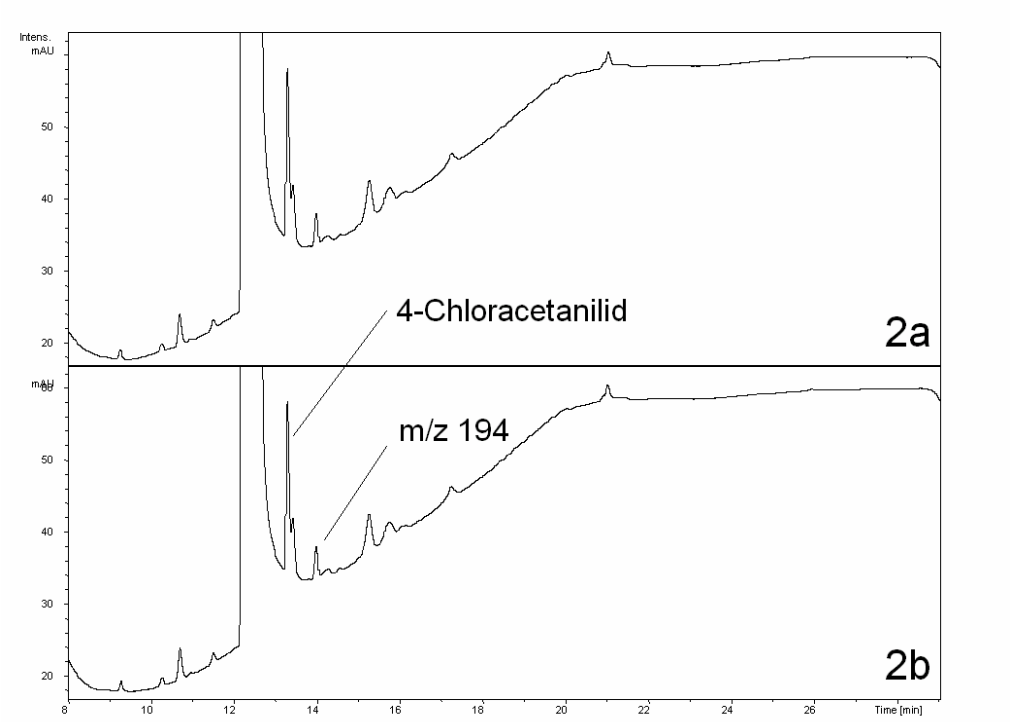

Figure 2 HPLC/UV-MS-Analysis of phenacetin, method 1 (2a: reference sample for comparison; 2b: sample after exposure to methyl bromide)

Table 1 Reaction products in pharmaceuticals after exposure to methyl bromide

Sample	Exposition	Reaction product in comparison with the untreated sample
Chinin-HCl-H_2O (active ingredient)	80 g/m^3, 24 h, open	n.n. (< 0.08 %)
Diclofenac-Na (active ingredient)	80 g/m^3, 24 h, open	n.n. (< 0.06 %)
Salicyl acid (active ingredient)	80 g/m^3, 24 h, open	n.n. (< 0.07 %)
Phenacetin (active ingredient)	80 g/m^3, 24 h, open	n.n. (< 0.01 %)
Metformin-HCl (active ingredient)	80 g/m^3, 24 h, open	n.n. (< 0.08 %)
	80 g/m^3, 24 h, in double PE-bag	n.n. (< 0.08 %)
	80 g/m^3, 24 h + 50 ppm, 3 weeks	n.n. (< 0.08 %)
Procain-HCl (solution)	80 g/m^3, 24 h, unopened	impurities with mol mass 323: increase of 0.04 %, other reaction product n.n. (< 0.02 %)

Table 2 Reaction products in pharmaceuticals after exposure to methyl bromide (HU)

Active ingredient	Matrix	Bromide µg/g	
		untreated	fumigated (24 h)
Chinin-HCl.2H_2O	powder	2.2	13
Diclofenac	powder	n. n.	5.7
Phenacetin	powder	n. n.	156
Procain 2% Steigerwald	solution	n. n.	n. n.
Salicylacid	powder	n. n.	n. n.
Metformin HCL	powder	8	8.9 (24 h) 8.3 (24 h in bag) 8.7 (after 3 weeks)

n. n. – non detectable (Limit: 1 µg/g, determination limit: 2 µg/g)

Table 3 Bromide content in pharmaceuticals after exposure to methyl bromide, determined with GC/MS-Analyse

active ingredient	Matrix	Bromide µg/g	
		untreated	fumigated (24 h)
Chinin-HCl.2H2O	powder	3.5	15.6
Diclofenac	powder	n. n.	5.5
Phenacetin	powder	n. n.	185.6
Procain 2% Steigerwald	solution	16.6	20.8
Salicylsäure	powder	n. n.	n. n.
Metformin HCL	powder	6.3	7.7 (24 h) 6.7 (24 h in bag) 5.8 (after 3 weeks)

n. n. – non detectable (determination limit: 1.5 µg/g)

Comparing the detected bromide contents with the ADI showed that even in extreme cases of a suspected fumigation of pharmaceuticals only 1% of the ADI is covered (Table 4).

Table 4 Risk assessment for bromide in pharmaceuticals

Pharmaceutical	**daily dose [g/d]**	**bromide-content [µg/g]**	**uptake [µg br/d]**	**uptake [µg br/kg bw/d]**	**ADI [µg br/kg bw/d]**	**ADI-part [%]**
Diclofenac	0.2	5.7	1.1	0.023	400	0.006
Phenacetin	0.75	185.6	139	3.0	400	0.75
Chinin-HCl	2	13	26	0.55	400	0.14

explanation:

bw = body weight
ADI = acceptable daily intake
br = bromide
row 2: upper limit of the recommended daily dose
row 3: bromide content in pharmaceutical after the fumigation
row 4: bromide intake estimated on the base of the daily dose
row 5: bromide intake per kg bw on the base of 100% oral resorption, bw 47 kg (5. percentile for adult women)
row 6: tolerable daily intake [EMEA 1997]
row 7: part of the daily acceptable intake

4. Discussion and Conclusion

In non of the investigated pharmaceuticals reaction products could be detected which might have been produced during the 24 hour exposure to high concentrations of methyl bromide. Even in the procaine containing solution the increase of impurities from 0.06% in untreated to 0.1% in fumigated samples is presumably not related to the reaction with methyl bromide.

One should consider that the exposure of the open solution is not very realistic, but still did not show a significant change.

In preliminary investigations for this study also no changes or productions of more than 1% could be detected and the changes could never clearly be contributed to the exposure to methyl bromide.

In three products the bromide content increased slightly. Since bromide belongs to the typical food components the detected increased amounts were far below 1% of the ADI.

The results of this study do not show any hint for health hazards or risks from fumigation of pharmaceuticals with methyl bromide in containers.

5. References

ISPM15, International standards for phytosanitary measures. http://www.ispm15.com

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