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LETTER TO THE EDITOR

Can humans metabolize arsenic compounds to arsenobetaine?

Dear Sir,

Goessler and co-workers[1] used the apparent accidental exposure, by inhalation, to trimethylarsine (or, more improbably, arsenic trichloride) of a subject whose arsenic excretion they were monitoring, to account for the appearance of inorganic and methylated arsenic compounds (including arsenobetaine) in the subject's urine. I think the explanation offered by Goessler *et al.* for the pattern of arsenic compounds in the subject's urine is improbable and I offer an alternative explanation.

The data and Goessler's explanation

The volunteer's first urine of the day was monitored from 2 to 23 October 1995. The authors report a possibility that he might have been exposed to arsenic (trimethylarsine) by inhalation on 10 and 11 October (student synthesis) and on 12 and 13 October (his own synthesis). He ate fish for lunch on 6 October and 19 October. The results for arsenic excreted in the first urine of the day (μg As/g creatinine) are presented for 2 October to 23 October for arsenite, arsenate, methylarsonic acid (MAA), dimethylarsinic acid (DMAA) and arsenobetaine, and for the sum of these compounds. No data are presented for trimethylarsine oxide (TMAO) and we must assume that it was not detected. For all reported arsenic species (except arsenite, and MAA after the fish meals), there are elevations in urine concentrations apparently associated with these three events (the fish meals and the inhalation).

We are concerned here only with the supposed workplace exposure. Goessler and colleagues suggest that inhalation of trimethylarsine gave rise to elevated levels of arsenate, MAA, DMAA and arsenobetaine in the urine. This means that two things must have happened — trimethylarsine must have been demethylated and oxidized (to yield arsenate, MAA and DMAA) and, probably independently, it must have acquired the carboxymethyl group necessary for conversion to arsenobetaine. Both of these seem to me unlikely. Several publications (e.g. Refs[2–6]) have reported results which demonstrate the stability of the arsenic–carbon bond in mammalian systems. Although only one of these[6] has, to my knowledge, dealt specifically with trimethylarsine, they are all likely to be relevant to the current issue. Those few reports[7–9] employing highly sensitive techniques that do offer evidence of demethylation in mammalian systems show only trivial amounts of demethylated products compared with those reported by Goessler *et al.*

The presence of trimethylarsine oxide (TMAO), the most likely metabolite of trimethylarsine, was not reported in the urine of the volunteer. Yamauchi *et al.* showed[6] that trimethylarsine administered to mice and hamsters was metabolized to TMAO. It is unlikely then that any trimethylarsine administered to, or inhaled by, humans would be converted to arsenobetaine and none to TMAO. It has also been reported[10] that TMAO administered orally or intraperitoneally to the hamster is excreted unchanged and no evidence was reported of its conversion to arsenobetaine.

An Alternative Explanation

From the quantity of arsenic attributed to the workplace exposure, as revealed by the figures in the paper and assuming a total daily excretion of creatinine of 1.2 g,[11] we can estimate a total arsenic excretion of very approximately (all compounds) 130 μg. It is difficult to believe that a worker, presumably taking all reasonable precautions when handling a toxic substance and carrying out the operation in an efficient fume hood, could inhale enough arsenic to excrete 130 μg in his urine. Presumably he would only inhale a small proportion of that in the atmosphere of the room, and he would exhale a substantial proportion of the quantity inhaled. To excrete 130 μg of arsenic through the kidney seems to me to be evidence of substantial contamination.

The pattern of excretion is strange. High levels of arsenate, MAA and DMAA were found in the morning urine of 12 October, *before* the volunteer had started his own synthesis and when exposure could apparently only have resulted from his indirect contact with the preparation of the graduate student.

Arsenobetaine was excreted, starting on 13 October, in a pattern which indicates a single dose

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on 12 October. Indeed, the pattern of excretion was almost identical to that following the first fish meal (that taken on 6 October). So, was arsenobetaine built up in the body, then suddenly excreted from 13 October onwards, even though the patterns of excretion of the other arsenic compounds (all supposedly metabolites of trimethylarsine) were changing? This also seems unlikely.

I propose that there was no measurable workplace exposure but that the pattern of excretion of arsenic compounds by this volunteer strongly indicates a double exposure to arsenic, probably through the diet. First, I suggest an exposure to inorganic arsenic on 10 October (mineral water? medicine? tonic? contaminated foodstuff? wine? grapes or other fruit? health food? hand-to-mouth contamination?). The total dose would have been about 50 μg of arsenic. The subsequent pattern of excretion of methylated compounds (excluding arsenobetaine) is consistent with a single dose of inorganic arsenic.[12–15] (The diagrams for arsenic excretion for 2 to 23 October when there was no experimental dosage suggest unknown, low-level, presumably dietary, exposure to inorganic arsenic.)

The volunteer would then have received a single dose of arsenobetaine, presumably in his food, on 12 October. The quantity of arsenic (about 80 μg) does not suggest a large fish meal — that much arsenic as arsenobetaine could easily be contained in a single small shrimp (although the amount of arsenobetaine excreted is very similar to that excreted following the first fish meal as noted above) — but might suggest some fishy component to a meal such as a sauce or meat of an animal fed on fish meal, or, indeed, it might have come from mushrooms or other unidentified terrestrial source.

Clearly, the authors have not demonstated that trimethylarsine is metabolized to arsenobetaine (indeed they do not make such an explicit claim) and I believe there is a more reasonable explanation for the pattern of excretion of the arsenic compounds that they report. The authors are generally careful to show that they are offering a speculative explanation. Nevertheless, the last two sentences of the paper state that, 'The results strongly indicate that the human body can do more than form methylarsonic acid and dimethylarsinic acid. It most probably can demethylate organic arsenic compounds and can synthesize arsenobetaine when appropriately challenged.' And they make the claim in their Discussion section that the source of arsenic was established, almost (it might be taken) as part of the experimental protocol. This was clearly not the case; '… the much more volatile trimethylarsine, to which the volunteer was exposed during the distillation… delivered most of the arsenic detected in the urine. The trimethylarsine present at traces in the laboratory air must have entered the body via the lung.' How could the authors possibly know this if arsenic in the laboratory air was not measured? There was no report of this.

In summary:

- No TMAO was reported in the urine of the volunteer.
- The time pattern of excretion of arsenic compounds suggests a double exposure.
- The pattern of inorganic and methylated compounds (MAA and DMAA) resulting from the first of these exposures is consistent with a single dose of about 50 μg of inorganic arsenic.
- The time pattern (in particular the shape of the 'decay' curve) suggests the second exposure was to arsenobetaine in a single dose of at least 80 μg.
- Upwards of 130 μg As in the urine is probably too much for accidental exposure through inhalation when an efficient fume hood is employed.

The explanation I offer relies upon the dietary intake of two small but significant amounts of arsenic at about the time that the volunteer was in the vicinity of trimethylarsine syntheses. Furthermore, these postulated intakes were not apparently evident from the dietary records of the volunteer and were therefore unexpected. I suggest, though, that my explanation is less improbable than that offered by Goessler and his colleagues. The latter is contrary to the outcome of previous work and, at this time, seems based upon little more than circumstantial evidence.

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