relative risk for lung cancer of 1.7 (95% CI 0.7–4.0).⁸ This increased value, however, was not confirmed by a second follow up as the relative risk decreased to 1.2 (95% CI 0.6–2.2).⁸ These results remained unchanged after adjustments for smoking.⁹ Moreover, with an external reference, the lung cancer SMR of SS welders was low (1.13 (95% CI 0.67–1.91)).⁹

The case-control study by Hull *et al* in Los Angeles county¹⁰ showed ORs of 0.9 (95% CI 0.5–1.8) for SS welders and 1.3 (95% CI 0.6–2.3) for SS welders predominantly exposed to hexavalent chromium and nickel (manual metal arc welders), whereas the OR was 1.6 (95% CI 0.8–3.1) for MS welders. Adjustments for smoking made little difference.¹⁰

The European mortality study included 11 092 welders from eight countries.¹¹ This large study provided no consistent difference between MS welders, for which the SMR was 1.78 (95% CI 1.27–2.43, statistically different) and predominantly SS welders whose SMR was 1.23 (95% CI 0.75–1.90). The results of this study for cancer incidence provided the same pattern as those for mortality as the standardised incidence ratios (SIRs) of lung cancer were 1.75 (95% CI 1.22–2.42) for MS welders and 1.39 (95% CI 0.74–2.38) for predominantly SS welders.¹²

In conclusion, it seems to me that, although SS welders are potentially exposed to chromium and nickel compounds,⁷ epidemiological studies focused on the risk of lung cancer of SS welders do not provide clear evidence to suggest that SS welders are at higher risk of lung cancer than MS welders. Therefore, the cause of the excess lung cancers found among MS and SS welders is an unanswered issue.⁵ A recent study by Jockel *et al* supports the hypothesis that some of the excess risk of lung cancer among welders could be due to exposure to asbestos.¹³ Further investigations that controlled for smoking, exposure to asbestos, and possible differential healthy worker effects among MS *v* SS welders,¹¹ are needed.

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Vandœuvre

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Urinary N-acetyl-β-D-glucosaminidase (NAG) and exposure to inorganic lead

Editor—Urinary activity of N-acetyl-β-D-glucosaminidase (NAG) had been reported to be one of the earliest markers to be increased in workers exposed to lead.^{1–4} The underlying mechanism for an increase in NAG activity is yet to be elucidated. It was suggested that the increase in NAG activity may be due to stimulation of exocytosis.⁵ In a recent publication⁶ based on workers from a lead smelting plant, it was further suggested that increase in NAG activity among workers exposed to lead was due to concomitant "albeit slight cadmium exposure". Their conclusion was based on the finding that urinary cadmium concentration (CdU) was the only significant variable in explaining the variation in NAG activity through stepwise regression analysis. Furthermore, the correlation coefficient (*r*) between NAG and CdU, was 0.41 in the non-exposed and 0.35 among the exposed workers.

Our data from exposed workers in a polyvinyl chloride lead stabiliser plant did not support this hypothesis. The increases in NAG, the heat labile isoenzyme (NAG-A), and the heat stable isoenzyme (NAG-B) were all highly associated with the recent change in blood lead (PbB) concentration over the past six months (PbBΔ).⁴ Among several exposure indices derived from serial PbB concentrations, PbBΔ was the only significant variable to account for the variation in NAG, NAG-B, and NAG-A. Furthermore, CdU and blood cadmium (CdB) did not correlate well with NAG and its isoenzymes. When they were forced into

the regression model, CdU was in fact negatively correlated (table). Activity of NAG is also increased when other xenobiotics affect the proximal tubules.^{7–9} It is indeed very unlikely that NAG is a specific marker for cadmium. As inorganic lead is known to cause proximal tubular dysfunction, it is therefore not surprising to see an association between lead exposure and NAG.

Among lead smelters, it is possible that there may be significant concomitant exposure to cadmium. This is evident by the fairly wide range of CdB results (0.3 to 5.9 µg/l) and the significantly higher CdB and CdU concentrations among the workers exposed to lead.⁶ Our cohort of PVC lead stabiliser workers had never been exposed to cadmium. Their geometric mean (range) CdB and CdU were much lower than those of the lead smelters (CdB: 0.56 (0.10 to 1.92) µg/l; CdU 0.41 (0.12 to 2.07) µg/g creatinine). We have also previously reported that NAG activity was better correlated with CdB and about 40% of the workers exposed to cadmium with a CdB of less than 3.0 µg/l had increased NAG concentrations.¹⁰

Hence it is possible that where there is significant cadmium exposure, cadmium plays a greater part in increasing NAG activity than does lead, and perhaps even masks the contribution of lead. Our data show that lead does increase NAG activity in the absence of cadmium exposure.

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Contribution of PbBΔ, CdB, and CdU to variation in NAG*

Independent variables	Partial regression coefficients (β) (95% CI)	Unit free β	r ²
Total NAG:			
PbBΔ	4.12 (2.22 to 6.01)	0.63	0.45
CdB	0.16 (–0.08 to 0.40)	0.19	
CdU	–0.14 (–0.31 to 0.04)	–0.22	
NAG-B:			
PbBΔ	11.9 (5.96 to 16.43)	0.66	0.43
CdB	–0.45 (–0.95 to 0.05)	–0.28	
CdU	–0.03 (–0.39 to 0.34)	–0.02	

*Multiple linear regression analysis with log transformed data.

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Author's reply

Editor—As early as 1981 we pointed out that an increased urinary excretion of lysosomal enzyme activity of renal tubular origin (β -galactosidase) should be cautiously interpreted as an early marker of proximal tubular dysfunction associated with exposure to lead (Pb) and cadmium (Cd).¹ Indeed, exposure to both metals, albeit at different intensities, usually occurs simultaneously both in industry and in the general population. Buchet *et al* clearly showed by a two way analysis of variance that in a group of 62 workers with mixed exposure to Pb and Cd, a moderate exposure to Pb had no direct or synergistic action with Cd on several early markers of nephrotoxicity including urinary activity of β -galactosidase. The renal changes were associated with Cd exposure only.

N-acetyl- β -D-glucosaminidase activity in urine (NAG), another lysosomal enzyme, can also be used as a sensitive marker for detecting proximal tubular toxicity in several situations likely to affect the integrity of the kidney.² Significant dose-response relations between NAG and the urinary concentration of Cd (CdU) have been reported in study populations with occupational³⁻⁶ or low level environmental Cd exposure.⁷ Several earlier cross sectional studies on workers moderately exposed to Pb showed that on a group basis there was some evidence of increased NAG compared with controls.⁸⁻¹¹ There is some doubt that these findings were directly related to Pb exposure, because these studies failed to show significant dose-response relations between NAG and the blood lead concentration (PbB) or duration of exposure to lead, and they did not take into account the effect of potential concomitant exposure to Cd (even low environmental Cd exposure).

Recently Chia *et al* have reported on the NAG isoenzyme profile in the urine of workers who manufactured Pb stearate stabilisers.¹² The urinary activity of NAG (total), NAG-A, or NAG-B did not show any relation with current or time-integrated PbB, but were all highly associated with the change of PbB over the past six months (Δ PbB expressed as percentage change). This finding was interpreted as the evidence that increased urinary NAG activity (NAG, NAG-A, NAG-B) could reflect recent changes of PbB. The authors did not support their explanation by checking whether the changes (Δ) in NAG activity over the same past six months. Also they did not measure biological variables of exposure to Cd at the time of their study, except blood cadmium (CdB) in a subsample of the non-exposed group. It is unclear whether the measurements of CdB and CdU used in the correlation study with total NAG and NAG-B reported in Chia's letter are related to the same initial study population and the same

period of time. The most disturbing finding of Chia *et al* is that urinary NAG activity is related to the percentage change in PbB without being correlated to the absolute Pb concentrations in blood.¹² This finding, which implies that the effects of Δ PbB on NAG activity are independent of the PbB concentrations, is difficult to reconcile with the basic concepts of toxicology.

In a study on workers exposed to Pb from a Pb acid battery factory in which all subjects had a CdU below 2 μ g Cd/g creatinine (mean 0.36 μ g Cd/g creatinine in both the control and exposed groups) we could not find any difference in NAG between the control and exposed groups.¹³ The mean PbB in the battery workers (510 μ g Pb/l) was, however, 50% higher than that of the Pb stabiliser workers examined by Chia *et al*.¹² The hypothesis that NAG represents a specific renal marker associated with an early stage of tubulotoxic action of Pb exposure is also not supported by other independent studies performed in our laboratory and by the findings of other authors.

In the study by Gerhardtsson *et al* on moderately exposed Pb smelter workers,¹⁴ NAG did not correlate with variables that reflected current (PbB) or time-integrated Pb exposure such as cumulative PbB index or Pb concentration in bone. Our recent study on Pb smelter workers corroborates this conclusion,¹⁵ as a stepwise multiple regression analysis indicated the lack of a direct association between NAG and the concentration of Pb in blood, urine, or tibia. The only predictor variable that was found to be significantly correlated with NAG irrespective of whether the correlation was examined in the controls or the Pb workers was CdU (the slopes of NAG *v* CdU were similar in both groups). The concomitant Cd exposure in these Pb smelter workers was low as shown by the CdB and CdU values that were still within the limits of distributions usually found for groups from the population at large in Belgium. It is interesting to note, however, that the current exposure to Cd (reflected as CdB) and the renal burden of Cd (reflected as CdU) in the control group (geometric mean (range) CdB 0.6 (0.1 to 2.6) μ g Cd/l; CdU 0.53 (0.16 to 1.51) μ g Cd/g creatinine) are similar to those reported in Chia's letter for the Pb stabiliser workers (CdB 0.56 (0.10 to 1.92) μ g Cd/l; CdU 0.41 (0.12 to 2.07) μ g Cd/g creatinine).

Taken together, the results suggest that the direct relation between Pb exposure and NAG is still questionable, and it seems more likely that the renal burden of Cd, even at very low concentrations, may play a predominant part in the alterations of tubular lysosomes that result in the release of renal NAG in the urine. This hypothesis is supported by our previous findings from cohorts of different populations such as another group of Pb smelter workers,¹⁶ pregnant women,¹⁷ and the general population.⁷ In none of these studies did Pb exposure emerge as a determinant of NAG, but in all of them NAG positively correlated with CdU that reflected a low exposure to Cd. In two of these studies the subjects' CdU did not even exceed 2 μ g Cd/g creatinine.^{16,17} Furthermore, a recent study from our laboratory may provide some insight into the biological significance of this association.¹⁸ A dose related increase in the urinary activity of NAG-B (considered as

the lesional form of NAG) with CdU has been found that is already significant in a subgroup that excreted 0.5 to 2 μ g Cd/g creatinine. The existence of a specific association between the urinary activity of NAG-B and CdU with no detectable CdU threshold suggests that Cd may produce cellular changes in the kidney at urinary Cd concentrations presently considered as in the normal range for populations with only low environmental exposure to Cd.

All these results reinforce the interpretation that the alleged association between urinary NAG activity and moderate exposure to Pb reported by several authors is frequently due to the fact that these authors have neglected to take into account the slightly increased body burden of Cd that is a frequent finding in workers exposed to Pb.

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