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Commentary

Authors' response to 'Critical review of Clara cell protein: sound science?'

We appreciate the opportunity to respond to the commentary by Dr Bernard on the biomarker serum CC16. In any scientific debate, differences of opinion will exist regarding whether – and to what degree – a scientific tool is considered valuable. In our view, the science surrounding the use of CC16 as a biomarker of exposure to a variety of environmental chemicals and as a biomarker of respiratory health effects is still in its early stages. State-of-the-science reviews such as ours serve to highlight strengths and weaknesses for a given subject and to identify future research needs. We respond here to some key concepts raised in Dr. Bernard's commentary.

Biomarkers of exposure and effect

Dr Bernard suggests that we have confused biomarkers of exposure and biomarkers of effect in our review. Although certain biomarkers have been used consistently to assess chemical-specific exposures (e.g. urinary cotinine, urinary cadmium), others demonstrate effects (e.g. changes in white blood cell counts) that are not specific to exposure. Biomarkers of effect must be used with caution in inferring causality. Serum CC16 has been consistently used by Dr Bernard and colleagues as both markers of effect and exposure despite serum CC16 being neither specific for a given exposure or as a marker of a specific effect. We maintain that 'Changes in serum CC16 concentrations (either transient or chronic) are not specific to any one agent, disease state, or etiology' (LaKind et al. 2007).

Sufficiency of the serum CC16 database

Whether CC16 has been 'sufficiently' investigated is not related to the number of investigations, but rather to whether available studies provide a logically consistent body of data demonstrating how the putative biomarker varies with the exposure or effect of interest.

Dose–response

Although serum CC16 levels are consistently lower in smokers, there is still considerable overlap in serum CC16 levels between smokers and non-smokers (see Figures 2 and 3 in LaKind et al. 2007), and according to Shijubo et al. (1997), no dose–response relationship is present.

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Interpretation of serum CC16 levels

Disentangling the three main processes affecting serum CC16 levels – namely, production by Clara cells, diffusion from alveolar lavage fluid across the pulmonary epithelial barrier, and renal clearance – could improve the interpretation of serum CC16 data. However, given the present state of knowledge and existing uncertainties, we stand by our original conclusion that 'many of the critical issues... must be better understood before serum CC16 levels can have application as a biomarker of effect or exposure ....'

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