The Boldt affair – correcting a collective failure

To the Editor

Sir

Following this journal's principled initiative [1], a process was initiated leading to the retraction of a considerable body of studies reported by the German anesthetist Joachim Boldt. As a result, eleven reports addressing the safety and efficacy of hydroxyethyl starch (HES) have been removed from the medical literature [2,3], as part of a retraction of eighty eight Boldt publications, in the first instance because of a lack of ethics approval. In addition, besides the first study retracted by *Anesthesia & Analgesia* [4], a review on four other Boldt studies found that results were probably incorrect and manipulated [5]. An extensive inquiry by the Klinikum Ludwigshafen, Boldt's employer, and the responsible State Medical Association, the Landesärztekammer Rheinland-Pfalz has been underway for the past year [6], and has reportedly revealed further non-compliance with German medical law, including faults in study design and data classification [5] . An official report of this process is still awaited. Apart from the grievous breaches in ethical issues, readers of *Anesthesia & Analgesia* are entitled to feel doubts on the veracity of the many Boldt studies claiming to use albumin in cardiac procedures since 1999, when the Klinikum Ludwigshafen has confirmed that no albumin has been used in the hospital since that year [6].

The Boldt scandal's effect on the evidence base of the safety and efficacy of HES is substantial.The Table summarizes the effect of the inclusion or exclusion of Boldt's studies from recent meta-analyses on fluid therapies. The paucity of evidence for the use of HES has also been confirmed by a recent systematic

review. Two of these meta-analyses [7,8]were published before the Boldt affair and had indicated that all types of HES were associated with kidney damage , an effect which is heightened when Boldt's studies are removed from the analysis [8] [Table 1]. The collective failure underpinning the Boldt affair also includes the authorities responsible for the approval of these products on the market. The absence of any pro-activity from them on this matter has been notable. The United States Food and Drug Administration (FDA) has announced that it will conduct a workshop reviewing the safety of HES sometime in 2012 [9], but is awaiting the results of large scale clinical trials such as CHEST [10]. The kind of prudent precautionism characterizing recent drug withdrawals appears to be absent for HES. Similarly, the German authority BPHARM's statement that current HES products were approved with minimal clinical data and bridging studies with other HES products [11] appears to be counter to European Union policy, which requires new clinical trials for new chemical entities, as the HES manufacturers claim these agents are. All in all, quiescence appears to have settled on the controversial aspects of HES' precipitated by the Boldt scandal and other developments, and it is desirable that the long-ongoing investigations are brought to a speedy conclusion.

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Conflict of Interest: The author provides services to the Plasma Protein Therapeutics Association, which represents manufacturers of products which are market competitors of HES.

Table 1. Meta analyses on fluid therapy – Influence on Boldt retracted studies on outcomes

Meta Analysis	Reference	Boldt included	Boldt Excluded
Albumin and survival in ICU	Cir Care Med 2011;39:386-391	Albumin improves survival by 18%	Albumin improves survival by 26%
HES and mortality	Open Medicine 2009;3:196-209	HES increases mortality by 6%	HES increases mortality by 26%
HES and kidney function (post-op creatinine)	Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD007594.	Favours HES by 4%	Favours albumin by 5%

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