We greatly appreciate the interest in our study (Schomaker et al., 2013) in which we evaluated emerging biomarkers of liver injury in the human population and their response to accidental acetaminophen (APAP) poisoning. In response to our study, Jaeschke and McGill (2013) raised a very interesting point regarding the application of glutamate dehydrogenase (GLDH) as a potential biomarker of mitochondrial damage. In their recently published study (McGill et al., 2012), the authors provide elegant proof-of-concept data indicating that the APAP-induced GLDH serum concentration in mice was a consequence of initial mitochondrial dysfunction-induced enzyme release from mitochondria to the cytosol followed by leakage to systemic circulation from injured hepatocytes. On the other hand, the treatment with high doses of furosemide, a hepatotoxicant that does not cause mitochondrial dysfunction, elicited comparable histopathologic changes and ALT elevations as APAP treatment, whereas GLDH levels remained unchanged (McGill et al., 2012). To enable applying GLDH as a biomarker of mitochondrial dysfunction, Jaeschke and McGill (2013) stressed the need to eliminate the effect of GLDH “contamination” from intact mitochondria leaked to circulation from injured hepatocytes and released due to the freeze-thaw cycle of serum samples. Therefore, Jaeschke and McGill (2013) suggested removing mitochondria using >14,000 × g centrifugation of freshly drawn blood instead of a routinely used 3000 × g spin.

Although, as Jaeschke and McGill noted, the suggested >14,000 × g centrifugation of blood during sample preparation would not affect the interpretation of our study for GLDH as a specific biomarker of general hepatocellular damage, we believe that the evaluation of GLDH as a potential mechanistic biomarker of mitochondrial dysfunction in hepatocytes is warranted. Because the published proof-of-concept study is very limited, including only two hepatotoxicants (McGill et al., 2012), a detailed validation of serum sample preparation including GLDH analytical procedures to detect mitochondrial damage is necessary. In addition, an evaluation of a large set of hepatotoxicants with a broad range of toxic mechanisms is crucial to confirm the proof-of-concept study. If successful, the application of GLDH as a mechanistic biomarker would contribute to better understand the role of mitochondrial dysfunction in complex mechanisms of hepatotoxicity and facilitate the diagnosis and risk assessment of clinically relevant drug-induced liver injury.

REFERENCES

