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Significant levels of endogenous formaldehyde in humans – a potential driver of Fanconi anaemia?

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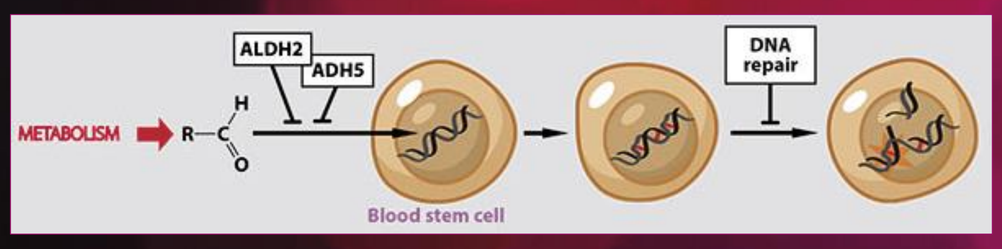
Background

Damage to our DNA can result in premature aging and cancer. This is exemplified by the genetic disease Fanconi anaemia (FA), a congenital bone marrow failure and cancer syndrome in children and young adults. The genetic mutations in FA result in deficiency in the FA DNA repair pathway, leading to breakages in chromosomes and sensitivity to DNA-crosslinking agents such as cisplatin.

The physiological cause of the DNA damage that drives bone marrow failure and an increased cancer risk in FA is not well understood. Recent advance using mouse models of FA have highlighted formaldehyde, a highly reactive by-product of metabolism, as the physiological genotoxin that drives the disease (Pontel et al., Mol Cell 2015; Burgos-Barragan et al., Nature 2017).

Mice deficient in both the FA pathway and Adh5, the enzyme that catabolises formaldehyde, present with a much more severe bone marrow failure and acute leukaemia phenotype, recapitulating the key features of human FA disease. We wanted to address whether levels of formaldehyde produced in humans could be high enough to drive FA. To this end, we set out to measure formaldehyde concentration in human serum.



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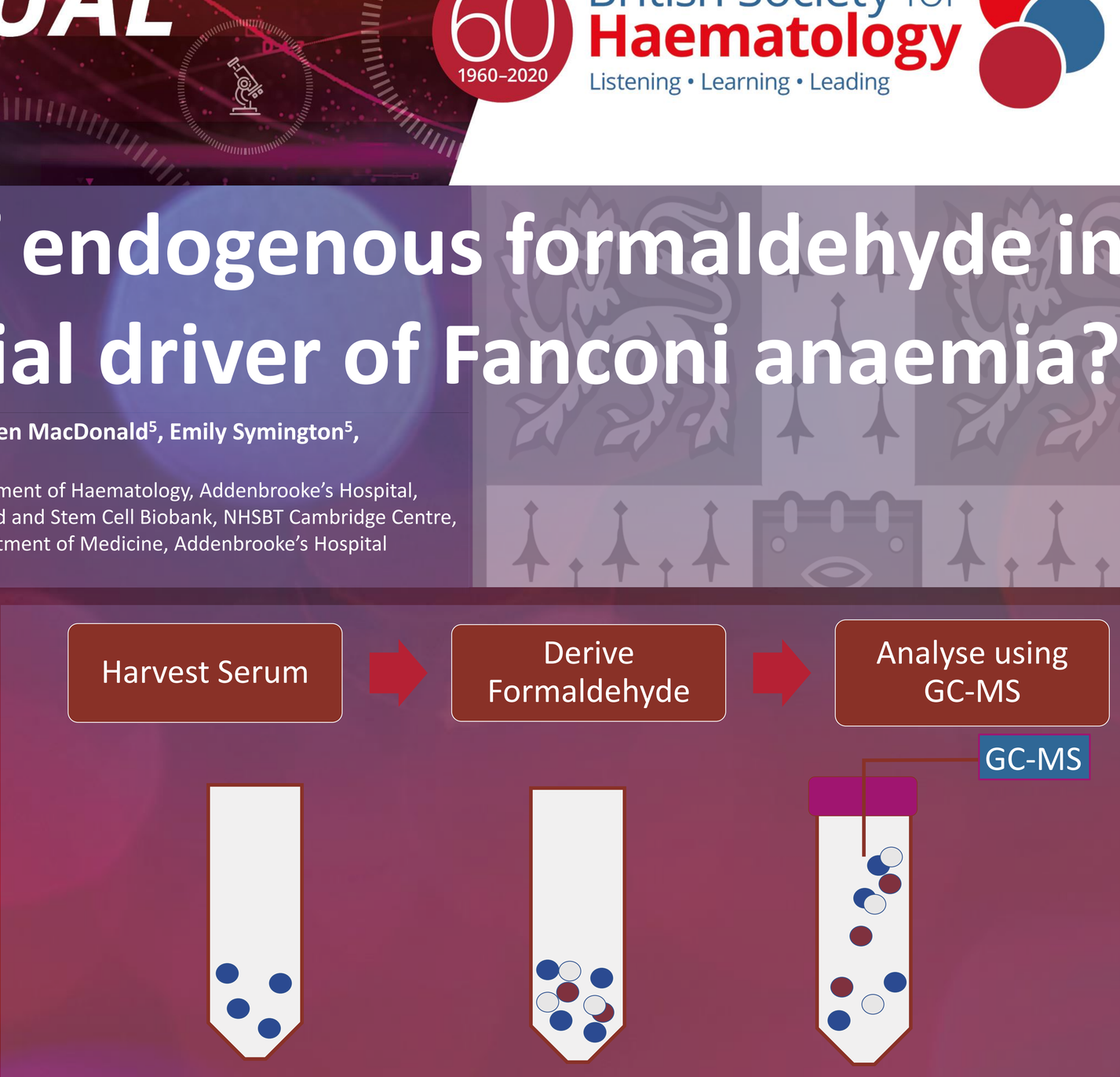
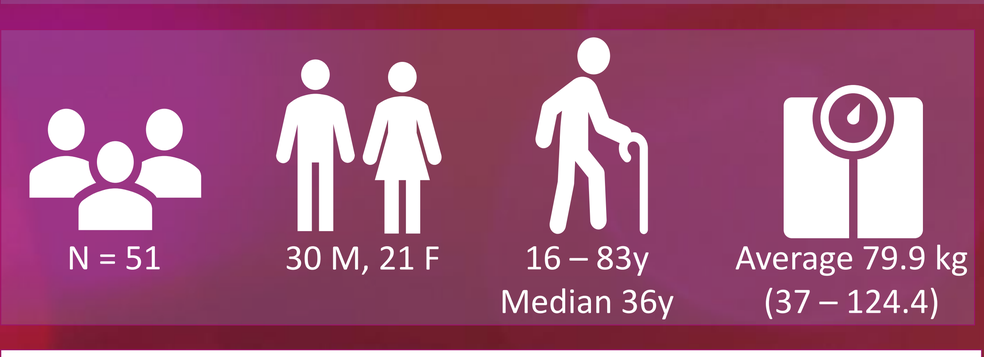
Method

Between September and December 2019, we consented and recruited 51 volunteers attending the haemostasis clinic at the Haemophilia Centre, Cambridge University Hospitals NHS Foundation Trust for investigation and management of bleeding disorders. None had a diagnosis of or were receiving active treatment for bone marrow failure syndromes or haematological malignancies.

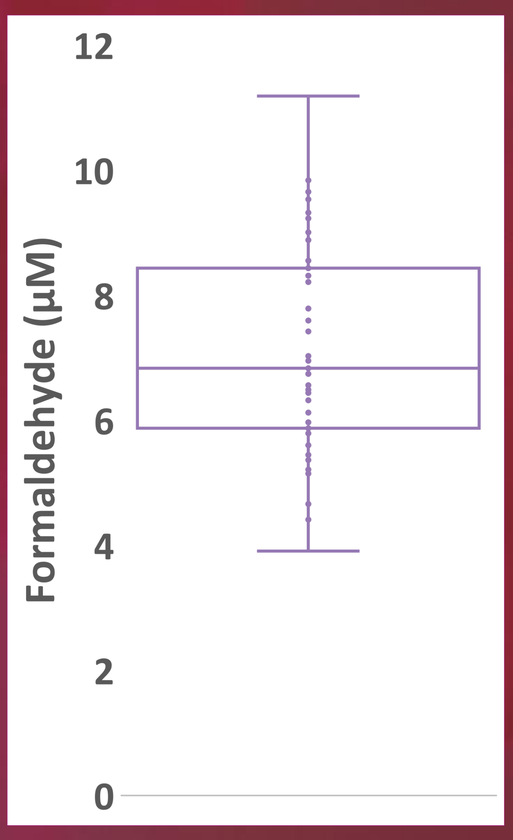


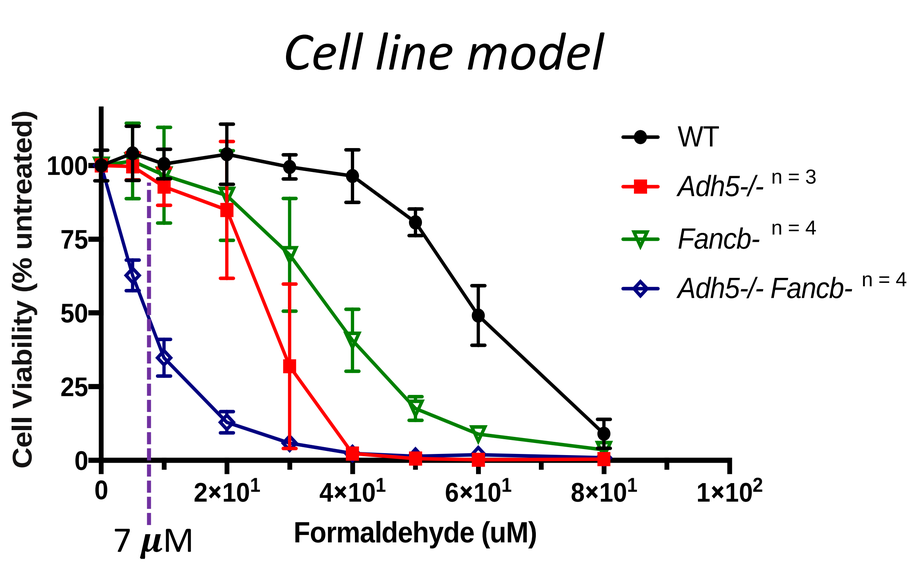


Results

Our results show an average serum formaldehyde of **7.1 µM** (*range 3.9 – 11.2 µM; 95% confidence interval 6.4 – 7.6 µM*). To assess whether this level of formaldehyde could affect cell viability, we measured growth of a haematopoietic cell line treated with formaldehyde for 4 days. The data suggests that a significant proportion of volunteers produced sufficient endogenous formaldehyde to pose a threat to cell growth in the absence of FA DNA repair and/or the Adh5 enzyme.

So far we have observed no correlation between serum formaldehyde and gender, weight, age, creatinine clearance, or serum liver enzymes.





Summary

We have been able to measure levels of formaldehyde in human serum and have found that it is present at concentrations that are able to cause in-vitro cellular toxicity if not protected by the FA DNA repair pathway.

It is therefore possible that formaldehyde is the major genotoxin driving development of human FA disease.

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