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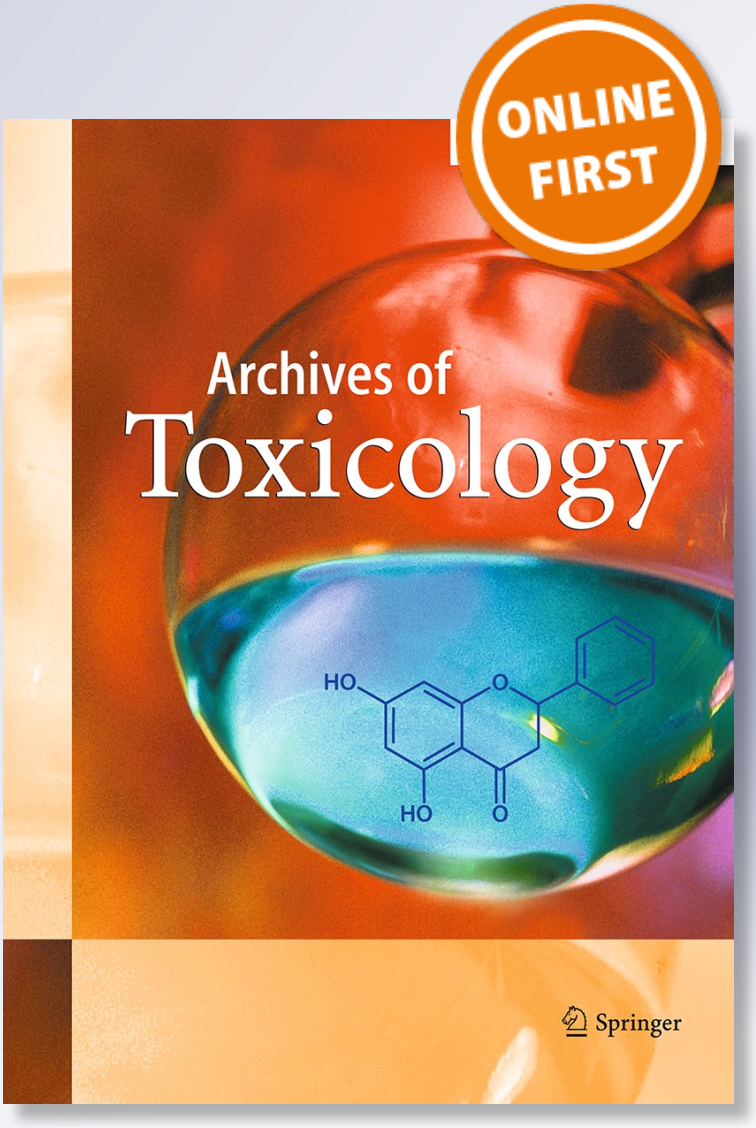

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REVIEW ARTICLE

Hypoxaemia affects male reproduction: a case study of how to differentiate between primary and secondary hypoxic testicular toxicity due to chemical exposure

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Abstract Classification for fertility is based on two conditions, namely on evidence of an adverse effect on sexual function and fertility and that the effect is not secondary to other toxic effects. To decide on an adverse effect is a relatively simple day-to-day decision in toxicology but whether this effect is secondary often leads to serious controversy. As the seminiferous epithelium operates on the verge of hypoxia, oxygen deficit can lead to secondary impairment of testicular function. This is well known from healthy mountaineers exposing themselves to high altitude. They have reduced blood oxygen content that goes in parallel with impairment of testicular function and this effect remains for some time in spite of a compensatory polycythaemia. Similar findings are described for experimental animals exposed to hypobaric oxygen/high altitude. In addition, testicular function is affected in severe diseases in humans associated with systemic oxygen deficit like chronic obstructive pulmonary disease, sickle cell disease or beta-thalassaemia as well as in transgenic animals simulating haemolytic anaemia or sickle cell disease. The problem of insufficient oxygen supply as the underlying cause for testicular impairment has received relatively little attention in toxicology, mainly because blood oxygen content is generally not measured in these animal experiments. The difficulties associated with the decision whether testicular toxicity is primary or secondary to hypoxia are exemplified by the results of inhalation studies with nickel subsulphide and gallium arsenide (GaAs). Both of these particulate substances lead to severe lung toxicity that might impair oxygen uptake, but testicular toxicity is only observed with GaAs. This may first be explained by different effects on the blood: nickel subsulphide inhalation leads to a compensatory erythropoiesis that may mitigate pulmonary lack of oxygen uptake. In contrast, GaAs exposure is associated with microcytic haemolytic anaemia thereby aggravating any possible oxygen undersupply. Furthermore, the predominant pulmonary effect caused by GaAs (but not by nickel subsulphide) is alveolar proteinosis. Pulmonary alveolar proteinosis is also known as a severe disease in humans associated with hypoxaemia. Therefore, we conclude that the testicular effects observed after GaAs are secondary to hypoxaemia caused by the combination of pulmonary proteinosis and haemolytic anaemia. This publication tries to raise awareness to the severe consequences of hypoxaemia on testicular function that may already be caused by reduced oxygen pressure at high altitude without any chemical exposure.

Keywords Hypoxia · Lung disease · Blood disease · Lung toxicity · Blood toxicity · Testicular toxicity · Male fertility · Gallium arsenide · Nickel subsulphide

Introduction

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