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Comment on "Comment on 'A Nested Case–Control Study of Serum Per- and Polyfluoroalkyl Substances and Testicular Germ Cell Tumors among U.S. Air Force Servicemen'"

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In their recently published letter to the editor,[1] Olsen et al. commented on the epidemiological study by Purdue et al.[2] and the accompanying "Invited Perspective" by Steenland.[3] The nested case–control study by Purdue et al. detected a positive association between the incidence rate of testicular germ cell tumors (TGCTs) and serum concentration of perfluorooctane sulfonic acid (PFOS) in active-duty U.S. Air Force servicemen. In their letter, Olsen et al. presented their animal experiment in which ∼41-d-old male Sprague-Dawley rats exposed to PFOS via diet for 104 wk did not show an increased incidence rate of testicular interstitial cell tumors, which are also known as Leydig cell tumors (LCTs).[1,4] However, the conclusion stated in their letter—namely, that their data "did not support a PFOS-related effect on testicular tumors in rats"[1]—warrants further clarification because the data presented by Olsen et al., which focus on LCTs, are only tangentially relevant to the study by Purdue et al., who focus on TGCTs.

First, an LCT is not a TGCT. Although both are "testicular tumors," their cell of origin is completely different. LCTs derive from somatic Leydig cells, whereas the vast majority ($>95\%$) of TGCTs are Type II germ cell tumors that originate from early-stage germline precursor cells—namely, primordial germ cells, or prospermatogonia.[5] It is not at all clear whether the absence of LCTs has any bearing on risk of TGCT. Although overgrowth of dysfunctional Leydig cells and increased TGCT risk is a sign of testicular dysgenesis syndrome,[6] the absence of an increase in LCT incidence rate after exposure of rats to PFOS has no appreciable relevance to human TGCT risk. Spontaneous or genetically engineered rodent models of TGCTs have been established,[7] but whether such models are suitable for assessment of the environmentally related risk of human TGCTs remains to be examined.

Second, the adequacy of the use of Sprague-Dawley rats for assessments of environmental risk factors of human LCTs has been repeatedly challenged based on differences in mechanisms of LCT carcinogenesis between rodents and humans as well as strong strain-specific differences in the incidence rate of spontaneous LCTs (e.g., age F344 male rats show an LCT incidence rate of $>80\%$[8]).[9–11]

Taken together, the comment by Olsen et al. needs to be interpreted cautiously, because the absence of an increase in LCT incidence rate in rats after exposure to PFOS has only tangential relevance to human TGCT risk.

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