ANDROGENIC (ANABOLIC) STEROIDS (Group 2A)

A. Evidence for carcinogenicity to humans (*limited*)

Cases of benign hepatoma, peliosis hepatis, primary hepatocellular carcinoma and hepatic cholangiocarcinoma have all been linked to the use of androgenic steroids, mostly oxymetholone[1-13]. At least 25 cases of liver-cell tumour have been reported in patients with Fanconi's anaemia[1-6,11,12], aplastic anaemia[1,4,7,8], paroxysmal nocturnal haemoglobinuria[1,12,13], panmyelopathy[9] or megaloblastic anaemia[10] treated with oxymetholone alone or in combination with other androgenic steroid drugs. Usually, treatment was given for years, but cancer has occurred within as little as two months of therapy[6], and there have been well-documented instances of remission following the withdrawal of oxymetholone treatment[8,9,11]. Hepatocellular carcinomas were also reported after extended treatment with oxymetholone of one patient with nephrolithiasis[14] and of another with chronic renal failure[15]; and hepatocellular carcinomas[1,16], cholangiocarcinomas[15] and adenomas[16] were reported after extended treatment of patients with methyltestosterone, testosterone oenanthate and nandrolone decanoate for hypogonadism[16], hypopituitarism[13], chronic renal failure[15] and generalized weakness[15].

The fact that castration palliates prostatic cancers suggests that testosterone may be involved in the genesis of these tumours[17], and a number of epidemiological observations suggest that increased testosterone levels may increase the risk for prostatic cancer. In addition, patients with cirrhosis, who have depressed testosterone levels[18], have low rates of prostatic cancer[19], and prostatic cancer is seemingly unknown among castrates[20]. There have also been a number of case reports[21-23] of prostatic cancer developing after androgen therapy; there was only one, unusual case, however, in which the cancer developed in a 'body-builder' at the age of 40 who had taken anabolic steroids for 18 years[23].

Blacks in the USA have the highest prostatic cancer rates in the world. Their two-fold increased risk, compared to US whites, is evident at the earliest age at which prostatic cancer occurs. Ross *et al.*[24] showed that young US blacks have a 15% higher mean testosterone serum level than young US whites, and argued that this difference could readily explain the two-fold difference in rates.

In one study[25], prostatic cancer cases were found to have higher mean levels of serum testosterone than healthy controls of the same age. Prostatic cancer cases in this study had a clear excess of high testosterone values. Another study [26] showed significantly higher levels of serum testosterone in prostatic cancer cases than in age-matched controls among US blacks, but not among African blacks. A number of case-control studies, however, showed no significant difference between cases and controls[27-29]. At present, there are insufficient data to permit firm conclusions to be drawn.

The development of myeloid leukaemia as a complication of Fanconi's anaemia has been reported in association with the use of oxymetholone[11,30,31], and there has been one case report of paroxysmal nocturnal haemoglobinuria in which a myeloproliferative disorder developed after oxymetholone therapy[32].

The evidence that anabolic steroids can cause both benign and malignant liver tumours is quite strong. However, because no analytical epidemiological study has been done, the Working Group felt constrained to classify the evidence for carcinogenicity in humans as no more than 'limited'.

B. Evidence for carcinogenicity to animals (*sufficient* for testosterone)

Testosterone propionate was tested for carcinogenicity in mice and rats by subcutaneous implantation, producing cervical-uterine tumours in female mice and prostatic adenocarcinomas in male rats. Neonatal treatment of female mice by subcutaneous injection of testosterone induced hyperplastic epithelial lesions of the genital tract and increased the incidence of mammary tumours. 5β-Dihydrotestosterone, which is considered hormonally inactive in adults, also increased the incidence of mammary tumours in mice when given neonatally by subcutaneous injection[33]. Depots of testosterone propionate implanted in rats resulted in an increased incidence of prostatic adenocarcinomas[34]. Subcutaneous administration of testosterone propionate following intravenous treatment with *N*-methyl-*N*-nitrosourea produced a high incidence of prostatic adenocarcinoma not seen with the individual compounds[35].

No data were available to the Working Group on oxymetholone.

C. Other relevant data

No data were available on the genetic and related effects of oxymetholone or testosterone in humans.

Testosterone did not induce sperm abnormalities or micronuclei in mice treated *in vivo* and was not mutagenic to bacteria[36].

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