# DUAL ACTION OF 2,3,7,8-TETRACHLORODIBENZO-*P*-DIOXIN IN THE NEONATAL MOUSE KIDNEY

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## ABSTRACT

**Dosage of mouse pups on days 0 or 1 of life with 2378-TCDD (20 μg/kg body weight) results in the development of hydronephrosis, as previously demonstrated. A hitherto unreported lesion characterised as an aplasia or agenesis of the ureteral-bud collecting system is described.**

## INTRODUCTION

The teratogenic effects induced by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2378-TCDD) in mice include cleft palate and cystic kidneys[1,2,3]. This latter lesion has been associated with the development of hydroureter[4]. *Hyperplasia of the ureteric epithelium is followed* by obstruction of the lumen, hydroureter, dilation of the renal pelvis and, ultimately, total destruction of the kidney parenchymal tissue.

Previous studies of this kidney lesion have involved dosage of the mother and the presumed transmission of 2378-TCDD to the foetus *in utero* or to the pup *via* the milk. In this presentation we describe an additional kidney lesion observed when mouse pups are dosed directly with 2378-TCDD after birth.

## EXPERIMENTAL PROCEDURES

Randomised litters of BALB/c, C57BL/10 or C57BL/10 x DBA/2 $F_1$ hybrid mouse pups were dosed with either 2378-TCDD (sc, 20 μg/kg body weight, 40 μM in DMSO) or with DMSO on day 0 or 1 of life. Alternatively, the pups were dosed daily with 0.5 μg/kg of epidermal growth factor (EGF) for 15 days. They were fostered onto a lactating female in a negative-pressure plastic-film isolator. They were killed by carbon

dioxide asphyxiation at intervals. Kidneys were fixed in buffered formalin and sections were stained with haematoxylin and eosin for microscopic examination.

**RESULTS and DISCUSSION**

The administration of 2378-TCDD direct to neonatal mice produces the same visible developmental changes as when it is administered *via* the maternal milk[5]. These are: a reduced rate of body weight gain, delayed hair growth, early eruption of incisors and precocious eye-opening.

If the 2378-TCDD-treated mice are kept after weaning they will develop a hydronephrotic syndrome in adult life. In some instances this will result in death associated with almost total destruction of the kidney parenchyma.

The kidneys of directly dosed animals will also show an inhibition of development affecting the glomeruli and the proximal tubules. In the kidney of a control mouse aged 3 weeks or more the glomeruli are all present well within the margin of the kidney, located in the main body of the cortex. In mice treated with 2378-TCDD there are many abnormal glomeruli and these are located on the margin of the kidney, directly beneath the capsule – *i.e.* there is no *cortex corticis* or outer, aglomerular zone of the cortex.

In older animals these alterations are associated with focal cystic changes which appear to be distinct from the hydronephrotic lesions.

This abnormality can be attributed to an arrest of the normal pattern of development. In the developing kidney, once the glomeruli are formed in the cortex further growth is by radial extension and convolution of the tubules, leaving the glomeruli embedded well within the cortex. In the treated mice some glomeruli are unaffected, as they have developed normally *in utero*, but others do not develop properly. Even after 104 days these abnormal glomeruli remain located on the outer surface of the cortex.

A parallel to this effect of 2378-TCDD in the neonatal mouse can be found in the adult rat. Cell division in the kidney following dosage with either lead or folate ion is inhibited by treatment with 2378-TCDD[6].

All of the visible developmental changes induced by 2378-TCDD match those caused by the administration of exogenous EGF[5]. It has not been possible to reproduce these kidney lesions by repetitive administration of EGF to the mouse neonates.

**CONCLUSIONS**

Treatment of neonatal mice with 2378-TCDD causes a kidney lesion characterised as a renal agenesis. It affects the glomeruli and proximal tubules. It is distinct from the previously reported hydronephrosis. This lesion can not be reproduced by the administration of exogenous EGF.

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