

EVIDENCE FOR THE MECHANISM OF ACTION OF THE  
2,3,7,8-TETRACHLORODIBENZO-*p*-DIOXIN-MEDIATED  
DECREASE OF NUCLEAR ESTROGEN RECEPTOR  
LEVELS IN WILD-TYPE AND MUTANT MOUSE HEPA  
1c1c7 CELLS

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**Abstract**—Treatment of wild-type Hepa 1c1c7 cells with 1 nM [<sup>3</sup>H]-17β-estradiol resulted in the rapid accumulation of the nuclear estrogen receptor complex whose levels were maximized within 1 hr. Cotreatment of the cells with 10 nM 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and [<sup>3</sup>H]-17β-estradiol did not affect the nuclear estrogen receptor levels 1 hr after addition of the radioligand; however, pretreatment of the cells for 1, 6, 24 or 42 hr with 10 nM TCDD prior to the addition of the radiolabeled hormone caused a greater than 50% decrease in nuclear estrogen receptor levels (determined by velocity sedimentation analysis) 1 hr after the addition of [<sup>3</sup>H]-17β-estradiol. In parallel experiments in which 10 nM TCDD was added 6 hr prior to the radiolabeled hormone, TCDD caused a 63 and 74% decrease in immunodetectable cytosolic and nuclear estrogen receptor protein levels, respectively, in the wild-type Hepa 1c1c7 cells. The nuclear estrogen receptor was also detected in two Hepa 1c1c7 mutant (class 1 and class 2) cell lines which have been characterized previously as TCDD non-responsive due to either decreased aryl hydrocarbon (*Ah*) receptor levels or a defect in the accumulation of transcriptionally active nuclear *Ah* receptor complexes, respectively. Treatment of these mutant cell lines with TCDD and [<sup>3</sup>H]-17β-estradiol (as described above) caused only a minimum (class 1) or non-detectable (class 2) decrease in nuclear estrogen receptor binding activity or immunodetectable protein levels. These results, coupled with the structure-dependent differences in the activities of TCDD (a strong *Ah* receptor agonist) and 2,8-dichlorodibenzo-*p*-dioxin (a weak *Ah* receptor agonist) in this assay system, support a role for the *Ah* receptor in the TCDD-mediated decrease of the nuclear estrogen receptor in mouse Hepa 1c1c7 cells. In addition, actinomycin D and cycloheximide both inhibited the TCDD-mediated decrease of nuclear estrogen receptor levels in the Hepa 1c1c7 wild-type cells, and these results suggest that TCDD may induce specific gene products which are involved in this process.