

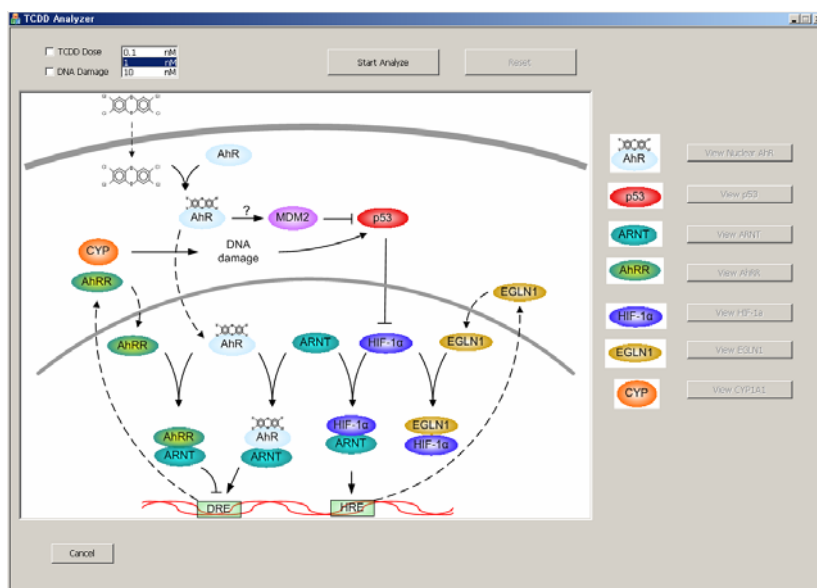
## *In Silico* TCDD Toxicity Evaluation System

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### Signal transduction pathways affected by TCDD

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is one specific type of polychlorinated dibenzodioxins (PCDDs). It gets bioaccumulated in animals due to its hydrophobicity, and is recently known as a potential carcinogen. Penetrating the membrane of a cell, TCDD binds aryl hydrocarbon receptor (AhR) with a strong affinity and thereby induces AhR in cytoplasm to move into nucleus. The AhR-TCDD complex needs to combine with aryl hydrocarbon receptor nuclear translocator (ARNT) to act as a transcription factor. This AhR-ARNT heterodimer transcribes a set of genes (cytochrome P450 family genes, AhRR, *etc.*) that have specific DNA sequences called dioxin response element (DRE) in their promoter regions [1, 2].

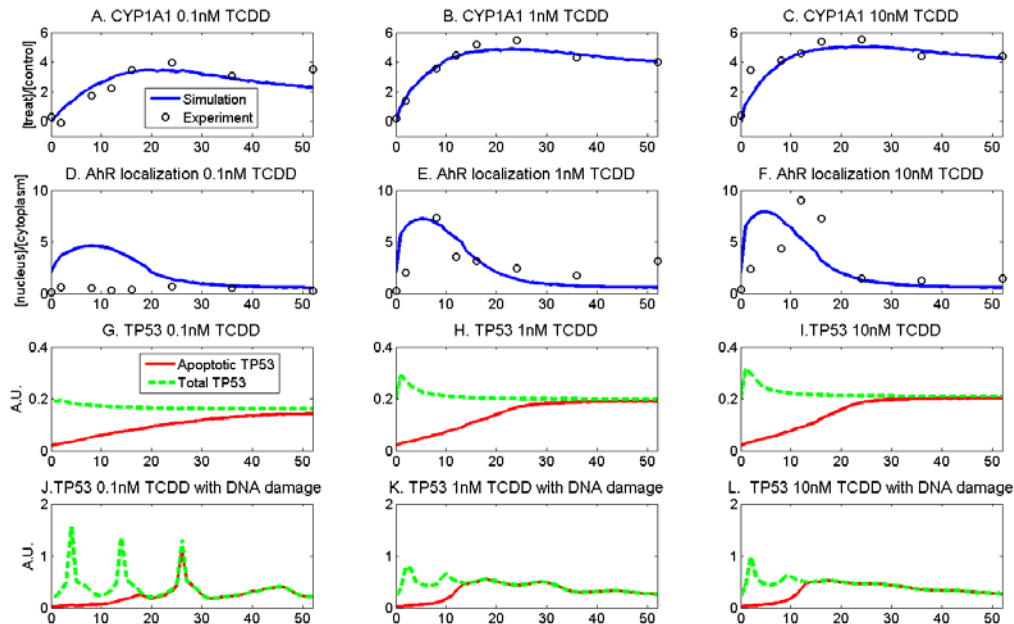


**Fig. 1** *In silico* TCDD toxicity evaluation system. It allows us to simulate the effects of TCDD on the signal transduction pathway of a human liver cell.

There have been some studies reporting that the TCDD-AhR complex inactivates p53 through activation of MDM2 [4] and that ARNT, which is the counterpart of AhR, binds with HIF-1 $\alpha$ , the well known hypoxia responding protein [5, 6]. These suggest that TCDD might have an effect on oncogenesis by disturbing the signal transduction pathways that were designed to react against DNA damages and hypoxia.

### Mathematical modeling and development of a graphical user interface

Conventional toxicology has been studied with experimental animals in general and it focuses on the relationships between intake dose of toxic materials and the corresponding lethal rates. In spite of the practical usefulness of this conventional approach, there are fundamental limitations on the experiments, logistics, and ethics related to the animal rights. Hence, there is a pressing need to develop a virtual model system that can be used for toxicity evaluation.



**Fig. 2** Simulation results. A, B, C: CYP1A1 simulation profiles and experimental results for each TCDD concentration level. D, E, F: AhR localization (AhR nucleus concentration/AhR cytosol concentration) profiles and the experimental results for each TCDD concentration level. G, H, I: TP53 simulation profiles for each TCDD concentration level without DNA damage. J, K, L: TP53 simulation profiles for each TCDD concentration level with DNA damage.

We have developed an *in silico* TCDD toxicity evaluation system (TES) based on an ordinary differential equation model and a systematic perturbation experiment of all the related signal transduction pathways. In the development, some direct effects of TCDD were referred to [3, 7]; hypoxia pathway was employed from [6]; the mathematical model of p53 pathway was employed from [8]. We have further estimated some kinetic parameters through curve-fitting of experimental profiles (Fig. 2A-F). We have also

developed a graphical user interface (GUI) to facilitate the evaluation of toxicity effects.

### Simulation results and concluding remarks

By using TES, we can simulate how the concentration profile of p53 changes according to the variation of DNA damage and TCDD intake. Without DNA damage, p53 level does not much change along with the TCDD intake, but it shows a quite different pattern in the case of DNA damage. In particular, the intake of TCDD lowers the total concentration of p53 while apoptotic p53 reacts faster. Fig. 2G-L show that cells are more likely to cause apoptosis for a high TCDD level, but they might have an effect on carcinogenesis for a low and steady TCDD level [3, 7].

### Acknowledgment

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