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# Discrimination between genotoxicity and cytotoxicity for the induction of DNA double-strand breaks in cells treated with aldehydes and diepoxides

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**Abstract**

The time-dependent dose–response relationships for the induction of DNA double-strand breaks (DSB) assessed by pulsed-field gel electrophoresis (PFGE) and for viability (evaluated by the MTT cytotoxicity test) were investigated in order to discriminate between genotoxic and cytotoxic mechanisms of DNA fragmentation. Cultured human lung epithelial cells (A549) were treated (i) with the aldehydes formaldehyde or glutaraldehyde and (ii) with the DNA–DNA interstrand crosslinkers melphalan, diepoxybutane or diepoxyoctane. Induction of DSB by formaldehyde and glutaraldehyde was seen only after cell viability was reduced to less than about 60% of the control values, indicating that DSB were the consequence of extragenomic damage and viability loss. Melphalan, diepoxybutane and diepoxyoctane induced DSB by a genotoxic mode with concentrations that did not affect cell survival: 8 h after treatment initiation both heat-labile crosslinks and DSB could be detected. Cells were not able to repair the crosslinks induced by diepoxybutane, the crosslinker with the shortest chain length. In contrast, with melphalan and diepoxyoctane, which have a longer crosslinking property considerable repair of crosslinks was observed. The molecular size distribution of the produced DNA fragments supported this mechanistic distinction. The DNA fragments generated by diepoxides were initially large, their concentration decreasing monotonously from 7 Mbp to less than 1 Mbp and were converted to smaller fragments by 72 h in the course of cell death. In contrast, DNA fragments induced by formaldehyde peaked below 1 Mbp, implicating activation of DNA-degrading enzymes. 

*Keywords:* Double-strand break; Aldehyde; Diepoxide

## 1. Introduction

DNA double-strand breaks (DSB) can be induced by a number of different pathways, so that their detection does not offer much insight into the mechanisms operating in their formation. However, for the assessment of the potential biological conse-

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