

MCB 110 Problem set 4. DNA repair -- **Answers**

1. Consider a bifunctional alkylating agent of the general structure $\text{Cl}(\text{CH}_2)_n\text{Cl}$ that attacks DNA. This agent can have the following consequences:
- (A) It can add to a base, B, to give the product $\text{Cl}(\text{CH}_2)_n\text{Cl}-\text{B}$. This is a monoadduct. In cases (B)-(E), a diadduct is formed.
- (B) It can add to two bases in the same strand of the double helix, B_{W1} and B_{W2} , to give $\text{B}_{\text{W1}}-(\text{CH}_2)_n-\text{B}_{\text{W2}}$
- (C) It can add to bases in the complementary strands of the double helix, B_{W} and B_{C} , to give $\text{B}_{\text{W}}-(\text{CH}_2)_n-\text{B}_{\text{C}}$
- (D) It can add to bases on different chromosomes in random positions, B_{I} and B_{II} , to give $\text{B}_{\text{I}}-(\text{CH}_2)_n-\text{B}_{\text{II}}$
- (E) It can add to the same base at the exact same positions in homologous chromosome, B_{M} and B_{D} , to give $\text{B}_{\text{M}}-(\text{CH}_2)_n-\text{B}_{\text{D}}$
- In each case, indicate which repair processes would likely be important in repair of the damage. Give your reasoning.

- 1A. Nucleotide excision repair. This system can remove modified nucleotides within a turn or so.**
- B. Nucleotide excision repair. Multiple rounds may be needed if n is large and the modified bases are far apart.**
- C. Double strand break repair mediated by recombination or end joining.**
- D. Successive nucleotide excision repair events, one on each chromosome.**
- E. Successive nucleotide excision repair events, one on each chromosome. (Can't use recombination because the same site is damaged on both chromosomes.)**

2. What is Loss Of Heterozygosity (LOH)? What are three mechanisms of LOH that contribute to cancer?

LOH is caused by gene conversion in which one of two alleles is lost. Three mechanisms of LOH include: 1) an independent mutation that inactivates the functional allele, 2) aberrant 3:1 chromosomal segregation in mitosis followed by loss of the chromosome carrying the unique allele(s), and mitotic recombination and normal segregation that redistributes the alleles. See Figure 23-11 in Lodish.

3. In double-strand break repair, why is the end joining pathway more mutagenic than homologous recombination?

The end-joining pathway causes deletions at the site of the join. In addition, the join can create new combinations of regulatory and coding sequences that cause inappropriate patterns of gene expression. In contrast, homologous recombination can result in the completely faithful restoration of the initial sequence.