Many decades of biophysical research provide compelling evidence that the *in vitro* and *in vivo* effects of radiation quality on cell death are closely related to the spatial distribution of energy deposits within targets smaller than the cell nucleus. Although cell- or tissue-level repair, tolerance and recovery mechanisms have the potential to amplify or suppress the effects of DNA damage, trends in double strand break (DSB) induction with radiation quality are often quite similar to the trends observed for chromosomal aberrations and reproductive cell death. As such, Monte Carlo simulations of the induction of clustered DNA lesions by ionizing radiation provide useful qualitative and quantitative information about the relative biological effectiveness (RBE) of proton and carbon ions compared to high-energy photons. We have recently modified the Monte Carlo Damage Simulation (MCDS) to account for reductions in the initial lesion yield arising from enhanced chemical repair of DNA radicals under hypoxic conditions. The kinetic energy range and types of particles considered in the MCDS has been expanded to include ions up to and including ^{56}Fe. Also, the MCDS now has the ability to simulate the induction of individual and clustered DNA lesions for arbitrary mixtures of the same or different types of particles under hypoxic and normoxic conditions.

For low linear energy transfer (LET) radiations, cells irradiated under aerobic conditions sustain about 2.9 times as many DSB as cells irradiated under anoxic conditions. Similar trends in the yields of non-DSB (Fpg and Endo III) clusters occur in HeLa cells irradiated by gamma-rays under aerobic and anoxic conditions. The differential effects of oxygen concentration on RBE increase with increasing particle LET. The RBE for DSB induction of a 1 MeV proton (26.9 keV/um) relative to ^{60}Co gamma-rays (0.24 keV/um) increases from 1.9 to 2.3 as oxygen concentration decreases from 100% to 0%. For comparison, the RBE for DSB induction of a 12 MeV ^{12}C ion (681 keV/um) relative to ^{60}Co gamma-rays increases from 3.4 (100% O_2) to 9.8 (0% O_2). Although the reported studies provide evidence supporting the hypothesis that DSB are a biologically critical form of clustered DNA lesion, other types of non-DSB cluster may still play an important role in reproductive cell death. The MCDS captures many of the essential trends in the formation of DSB and non-DSB clusters with radiation quality and oxygen concentration. The good agreement between measured and predicted cluster yields for DSB, Fpg and Endo III clusters suggests that, for the first time, it may be possible to determine nucleotide-level maps of the multitude of different types of clustered DNA lesions formed in cells irradiated under reduced oxygen. The MCDS is a useful computational tool to explore the interplay among radiation quality and the effects of tumor hypoxia in proton and carbon ion radiation therapy.

Learning Objective: To review, understand and quantify the effects of radiation quality and oxygen concentration on the induction of clustered DNA lesions by ionizing radiation