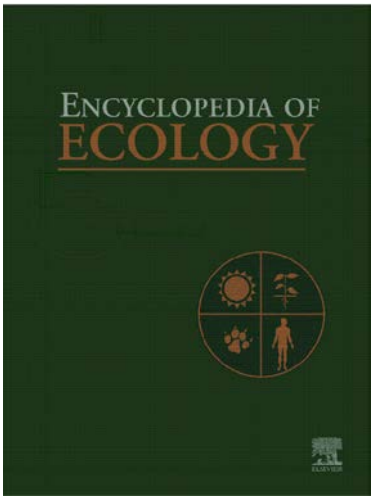

C W Theodorakis. Mutagenesis. In Sven Erik Jørgensen and Brian D. Fath (Editor-in-Chief), Ecotoxicology. Vol. [3] of Encyclopedia of Ecology, 5 vols.
pp. [2475-2484] Oxford: Elsevier.

sustainable expansions of the aquaculture operations of tomorrow, within their balanced ecosystem, to respond to a worldwide increasing seafood demand with a new paradigm in the design of the most efficient food production systems.

See also: Carrying Capacity; Energy Balance; Mariculture Waste Management; Monocultures Versus Polycultures; Technology for Sustainability.

Further Reading

Buschmann AH, Troell M, and Kautsky N (2001) Integrated algal farming: A review. *Cahiers de Biologie Marine* 42: 83–90.

Chopin T and Bastarache S (2004) Mariculture in Canada: Finfish, shellfish and seaweed. *World Aquaculture* 35: 37–41.

Chopin T and Robinson SMC (2004) *Proceedings of the Integrated Multi-Trophic Aquaculture Workshop*. Saint John, NB, 25–26 March 2004. *Bulletin of the Aquaculture Association of Canada* 104(3): 1–84.

Chopin T, Buschmann AH, Halling C, *et al.* (2001) Integrating seaweeds into marine aquaculture systems: A key towards sustainability. *Journal of Phycology* 37: 975–986.

Costa-Pierce BA (2002) *Ecological Aquaculture: The Evolution of the Blue Revolution*, 382pp. Oxford: Blackwell Science.

Fang J, Oivind S, Liang X, and Zhang J (2001) Carrying capacity and optimizing measures for mariculture in Sungo Bay. *Marine Fisheries Research* 22(4): 57–63.

FAO (2002) The state of world fisheries and aquaculture 2002. Food and Agriculture Organization of the United Nations, Rome, Italy; http://www.fao.org/docrep/005/y7300e/y7300e00.htm.

FAO (2004) The state of world fisheries and aquaculture 2004. Food and Agriculture Organization of the United Nations, Rome, Italy; ftp://ftp.fao.org/docrep/fao/007/y5600e/y5600e01.pdf

FAO (2006) State of world aquaculture 2006. Food and Agriculture Organization of the United Nations, FAO Fisheries Technical Paper 500, Rome, Italy.

Folke C, Kautsky N, Berg H, *et al.* (1998) The ecological footprint concept for sustainable seafood production: A review. *Ecological Application* 8(supplement): S63–S71.

McVey JP, Stickney RR, Yarish C, and Chopin T (2002) Aquatic polyculture and balanced ecosystem management: New paradigms for seafood production. In: Stickney RR and McVey JP (eds.) *Responsible Marine Aquaculture*, pp. 91–104. Oxon: CABI Publishing.

Naylor RL, Goldburg RJ, Primavera JH, *et al.* (2000) Effects of aquaculture on world fish supplies. *Nature* 405: 1017–1024.

Neori A, Chopin T, Troell M, *et al.* (2004) Integrated aquaculture: Rationale, evolution and state of the art emphasizing seaweed biofiltration in modern mariculture. *Aquaculture* 231: 361–391.

Ryther JH, Goldman CE, Gifford JE, *et al.* (1975) Physical models of integrated waste recycling-marine polyculture systems. *Aquaculture* 5: 163–177.

Tacon AGJ and Forster IP (2003) Aquafeeds and the environment: Policy implications. *Aquaculture* 226: 181–189.

Troell M, Rönnbäck P, Halling C, *et al.* (1999) Ecological engineering in aquaculture: Use of seaweeds for removing nutrients from intensive mariculture. *Journal of Applied Phycology* 11: 89–97.

Troell M, Halling C, Neori A, *et al.* (2003) Integrated mariculture: Asking the right questions. *Aquaculture* 226: 69–90.

Troell M, Neori A, Chopin T, and Buschmann AH (2005) Biological wastewater treatment in aquaculture – more than just bacteria. *World Aquaculture* 36: 27–29.

Mutagenesis

C W Theodorakis, Southern Illinois University Edwardsville, Edwardsville, IL, USA

Introduction
DNA Damage
Mutations
Effects on Fitness and Ecological Parameters
Further Reading

Introduction

Mutagenesis is the formation of mutations in DNA molecules. There are a variety of mutations that can occur in DNA, such as changes in the DNA sequence or rearrangement of the chromosomes. Such mutations may occur spontaneously, as a result of 'mistakes' that occur during DNA replication or mitosis. Spontaneous mutations are essential to produce genetic variation necessary for natural selection. Mutations may also occur as a result of environmental exposure to genotoxins (chemicals that alter the structure of DNA). Mutagenesis is of concern because it may lead to irreversible effects that can affect fitness of organisms, which in turn may affect population-level processes.

There are potentially thousands of mutagenic and genotoxic agents to which organisms are exposed. Examples of the classes of mutagenic compounds, the DNA damage they elicit, and their sources in the environment are listed in **Table 1**. Each genotoxin may elicit many different types of DNA damage.

DNA Damage

Types of DNA Damage

Because most environmentally induced mutations originate as DNA damage, any discussion on mutagenesis must begin with a discourse on this subject. For the sake of clarity, the structure of DNA bases is given in **Figure 1**.

Table 1 Examples of common mutagenic and genotoxic chemicals, their sources in the environment, and the mechanism of formation of DNA damage

Agent	*Environmental source*	*Damage caused*	*Mechanism*
Polycyclic aromatic hydrocarbons	Combustion of organic matter and fossil fuels, crude oil and coal spills and leaching, copier toner cartridges, coal coking, creosote, used oil and lubricants, asphalt	Adducts[a] Oxidative damage[a,b]	Metabolic activation Induction of cytochrome P450 Formation and redox cycling of quinones
Alkylating agents, nitrosamines	Rubber industry, dyes	Methylated or ethylated bases	Metabolic activation
Halogenated organics (PCBs, dioxins, chlorinated solvents, perfluorocarbons, brominated aromatic hydrocarbons)	Industrial manufacturing, paper processing, electrical insulators, cleaning and degreasing agents, solvents, chemical industry, combustion and manufacture of plastics, flame retardants, stain repellents	Oxidative damage[a,b] Adducts	Induction of cytochrome P450 Interference with mitochondrial function Modification of peroxisome function
Pesticides[c]	Agricultural, commercial, and residential applications	Oxidative damage[a,b]	Induction of cytochrome P450 Redox cycling (diquat) Interference with mitochondrial function Modification of peroxisome function
		Methylated or ethylated bases (some)	Metabolic activation
Transition metals, heavy metals, and arsenic	Industrial manufacturing, agricultural chemicals, ore mining and smelting, steel manufacture, building materials and paints, gasoline additives, fossil fuel extraction, combustion of coal, battery manufacture and disposal, metal plating, photographic emulsions, paper manufacture	Oxidative damage[a,b]	Reduction of O_2 to form superoxide[d] Reduction of hydrogen peroxide[d] Catalysis of quinone redox cycling[d] Interference with mitochondrial metabolism Inhibition of DNA repair Inhibition of antioxidant enzymes Glutathione depletion
		Adducts, cross-links (As, Cr, Pt)	Direct DNA binding
Ionizing radiation	Uranium ore mining and fuel processing, nuclear energy, nuclear weapons, combustion of coal	Oxidative damage,[a,b] base loss and fragmentation, DNA–DNA cross-links	Formation of oxyradicals from water and oxygen Excitation of oxygen to singlet oxygen Direct interaction of radioactive particle with DNA sugars and bases
UV light	Sun	Oxidative damage[a,b] Pyrimidine dimers, 6-4 photoproducts	Excitation of oxygen to singlet oxygen Interaction of UV light with bases

[a]Adducts and oxidized bases may lead to production of abasic sites via destabilization of the glycoside (sugar base) linkage.
[b]Oxidative damage includes oxidized bases, change in chemical structure of bases (e.g., open rings), strand breaks, base loss, DNA–protein adducts, and lipid aldehyde adducts.
[c]Includes insecticides (organochlorines, organophosphates, carbamates, pyrethroids), herbicides, and fungicides.
[d]Transition metals only.

Many classes of DNA damage can lead to mutations, as illustrated in **Figure 2**. Such DNA lesions include damage to DNA bases or to the deoxyribose sugar, base loss, strand breakage, and DNA cross-links (**Figure 2**).

Adducts

Numerous mutagens can form DNA adducts, which are molecules that form covalent bonds with DNA. Some chemicals transfer a methyl or ethyl group to a nucleotide base. **Figure 2b**, 1, illustrates a generalized structure of such a methyl-adducted base. Other chemicals form bulky adducts, so called because they are composed of relatively large and bulky molecules. A number of chemicals are not mutagenic in their native state, but require metabolic oxidation to convert them to mutagenic intermediates. These include polycyclic aromatic hydrocarbons

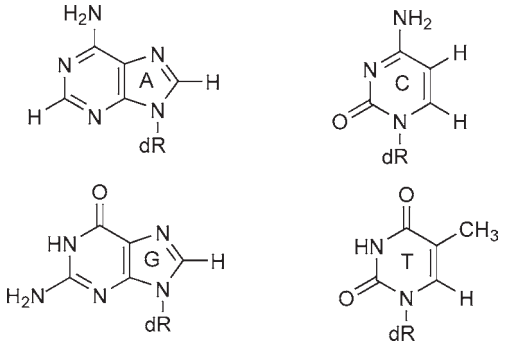

Figure 1 Schematic diagram representing the structure of DNA bases. A, adenine; C, cytosine; G, guanine; T, thymine.

(PAHs). **Figure 2b**, 2, is a schematic representation of a benzo[*a*]pyrene (a PAH that is a common environmental contaminant) adduct. Another type of adduct is lipid aldehyde adducts (**Figure 2b**, 6), which are formed as a result of oxidative damage to lipids, and are discussed in the next section.

Oxidative damage

Oxidative damage occurs as a result of interaction of free radicals or singlet oxygen (molecular oxygen in an excited state) with DNA. The most common oxyradicals include hydroxide radicals ($OH^{\cdot}$) and the superoxide anion O_2^{-}. Oxyradicals and singlet oxygen are potential mutagenic chemicals known as reactive oxygen species (ROSs). These ROSs are produced to some extent by endogenous metabolic processes, for example, during mitochondrial respiration, metabolism of natural and man-made hydrocarbons, and metabolism of fats. However, some chemicals may stimulate cells to overproduce ROSs metabolically. Besides metabolic processes, some hydrocarbons and heavy metals may convert molecular oxygen to superoxide.

ROSs can damage DNA in two ways. First, the ROSs themselves can form chemical bonds to nucleotide bases (**Figure 2b**, 3 and 4). Second, the oxyradicals may cause internal rearrangement of the DNA to form fragmented bases or open-ring structures (**Figure 2b**, 6). These ROSs may also react with cellular lipids or phospholipids, which leads to formation of lipid adducts (**Figure 2b**, 6). Finally, oxyradicals may oxidize proteins, creating protein radicals, which can form covalent attachments to DNA in the form of DNA–protein cross-links (**Figure 2b**, 8).

Base loss, sugar damage, and strand breakage

Base loss, sugar damage, and strand breakage may occur in several ways. For example, a base may be hydrolyzed from the deoxyribose sugar (**Figure 2c**, 9) enzymatically – during DNA repair (see below) – as a result of oxyradical attack, or as a result of bulky adducts or oxidized bases. This site is called an abasic site. Base loss can also occur as a result of free radical attack on the sugar, resulting in sugar damage (**Figure 2c**, 10). In addition, sugar damage may result in DNA strand breakage (**Figure 2c**, 11). Strand breaks may also be formed by hydrolysis of the sugar–phosphate bond (**Figure 2c**, 12). These types of strand breaks may be produced transiently during the DNA repair process. However, some chemicals might inhibit repair enzymes, resulting in persistent strand breaks.

Because DNA is a double-stranded molecule, strand breaks may occur in one (single-strand breaks, SSBs) or both of the DNA strands (double-strand breaks, DSBs; **Figure 3**). DSBs are less easily repaired and more persistent than SSBs, and are more effective in producing deleterious cellular effects. There are basically three ways in which DSBs may be formed. First, there may be two SSBs directly across from each other or in close proximity (**Figure 3**). Second, if an SSB is unrepaired and the cell tries to replicate a DNA molecule with an SSB, this may result in a DSB. Third, some types of enzymes can produce DSBs. If left unrepaired, DSBs can lead to chromosomal mutations, as discussed below, or may lead to cell death.

DNA cross-links

An additional class of chemically induced DNA lesions includes DNA cross-links. These are formed when some chemical agents such as *cis*-platinum (a chemotherapeutic agent), arsenic, or chromate can form adducts to two or more bases simultaneously. DNA cross-linking agents may covalently cross-link adjacent nucleotide bases on the same strand (intrastrand cross-links; **Figure 2c**, 15) or on opposite strands bases or (interstrand cross-links; **Figure 2c**, 16). Alternatively, cross-linking agents may link proteins to the DNA bases (DNA–protein cross-links).

Radiation-induced DNA damage

Chemicals are not the only environmental agents that can cause mutations. Radiation, a type of electromagnetic energy, may also be mutagenic. In general, there are two primary categories of mutagenic ionizing radiation and ultraviolet (UV) radiation. Although there have been claims that other types of electromagnetic energy – such as magnetic fields, microwaves, and radiowaves – are mutagenic or carcinogenic, to date, the evidence for this remains equivocal.

Ionizing radiation includes alpha particles (two protons and two neutrons, that is, a helium nucleus), beta particles (high-energy electrons), and gamma particles (high-energy photons). The sources of ionizing radiation in the environment may be natural or man-made. Natural sources include cosmic radiation – originating from the sun, stars, or other celestial bodies – and naturally occurring radioisotopes. Man-made sources are listed in **Table 1**. Ionizing radiation could produce base or sugar radicals, which are unstable and rapidly react with other

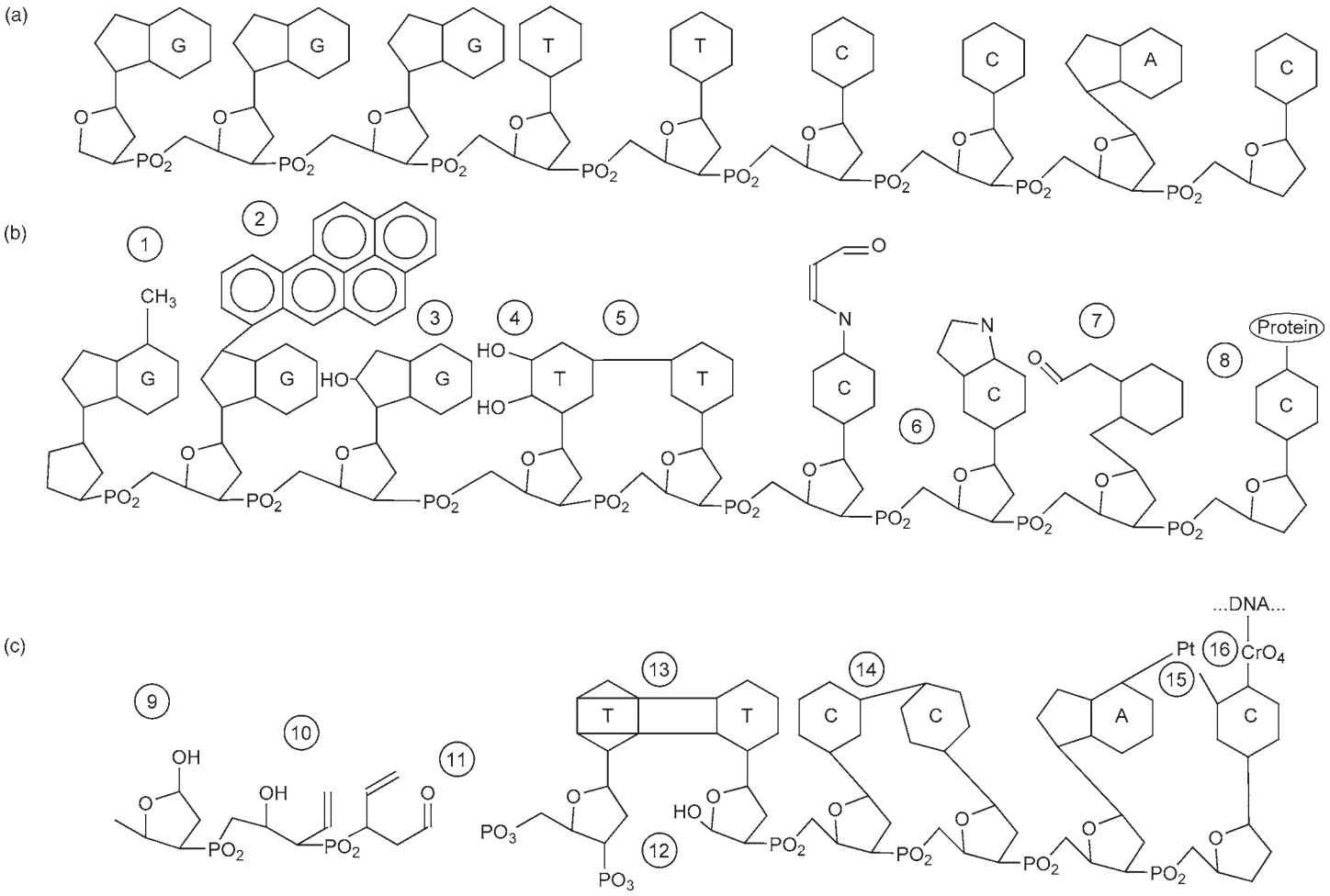

Figure 2 Diagram of the types of DNA damage that can occur as a result of exposure to genotoxic agents. (a) Undamaged DNA; (b) 1 – Methylated guanine, 2 – benzo[*a*]pyrene adduct, 3 and 4 – oxidized bases, 5 – DNA cross-link, 6 – two examples of lipid aldehyde adducts, 7 – open ring base, 8 – DNA–protein cross-link; (c) 9 – abasic site (hydrolysis of glycosidic linkage), 10 – sugar damage leading to base loss, 11 – sugar damage leading to strand break, 12 – hydrolysis of sugar–phosphate bond, 13 – thymine dimer, 14 – cytosine 6-4 photoproduct, 15 – DNA–DNA cross-link (interstrand), in this case mediated by *cis*-platinum (complete structure of *cis*-platinum not shown), 16 – DNA–DNA cross-link (interstrand), in this case mediated by chromate.

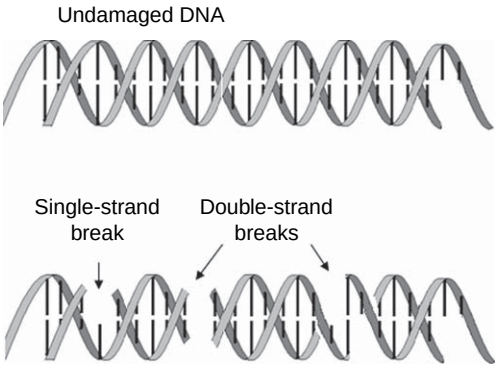

Figure 3 Schematic representation of DNA with single- and double-strand breaks.

macromolecules or undergo internal molecular rearrangements. This results in strand breakage, base loss, fragmented bases, DNA–DNA cross-links (**Figure 2b**, 5), or DNA–protein cross-links (**Figure 2b**, 8). Alternatively, the radioactive particles can interact with water or oxygen, which produces ROSs and singlet oxygen, which leads to oxidative DNA damage.

Another type of radiation is UV radiation. Because the source of UV radiation is the sun, environmental sources of UV radiation are entirely natural. However, anthropogenic activities may result in increased exposure or susceptibility to UV-induced mutagenesis. For example, chlorofluorocarbons (CFCs) may react with ozone in the upper atmosphere to convert it to molecular oxygen. Because ozone strongly absorbs solar UV light, this may result in increased UV reaching the Earth. Also, changes in climate (e.g., due to buildup of atmospheric CO_2) or draining of wetlands may lower water levels and expose aquatic organisms to more UV. Furthermore, some chemicals may inhibit an organism's natural ability to repair or prevent UV-induced DNA damage, or may react with UV to produce ROS.

UV can cause DNA damage in two mechanisms. First, UV can convert molecular oxygen into singlet oxygen (an energized, highly reactive form of oxygen). This may lead to increase oxidative DNA damage. Second, UV radiation can directly interact with DNA bases to produce so-called dimers and photoproducts (**Figure 2c**, 13 and 14, respectively).

Repair of DNA Damage

There are several different pathways involved in the repair of modified DNA bases. One such pathway is termed nucleotide excision repair, which repairs bulky adducts, lipid aldehyde adducts, and UV photoproducts (**Figure 4a**). A second type of DNA repair is termed base excision repair. This type of repair is used on oxidized bases, AP sites, methylated bases, and some SSBs,

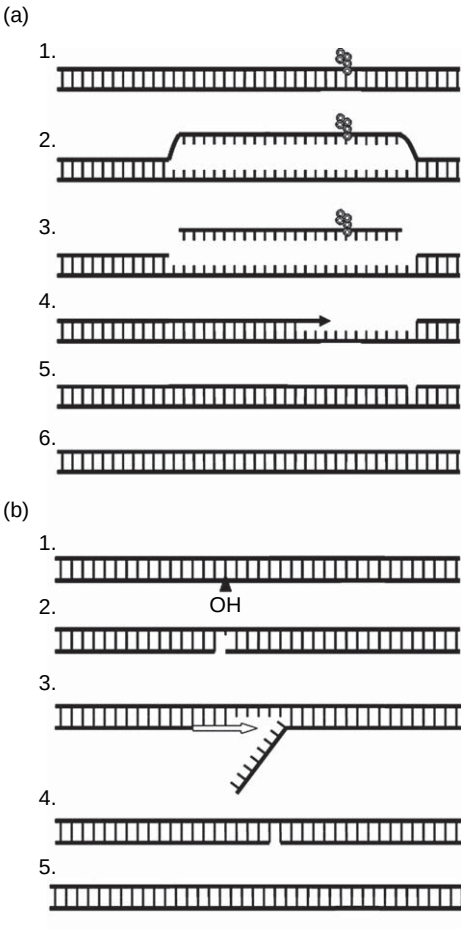

Figure 4 Methods of repairing damage to DNA bases. (a) Nucleotide excision repair: 1 – DNA with damaged base, 2 – damaged DNA is unwound and separated, 3 – damaged section is excised, 4 – gap is filled by DNA polymerase, 5 – single-strand gap remains after gap filling, 6 – ligase connects free ends. (b) Base excision repair: 1 – DNA with damaged base, 2 – damaged base is removed and nick is made in DNA, 3 – DNA polymerase simultaneously displaces damaged section (producing a 'flap') and synthesizes new DNA, 4 – flap is cut, leaving a single-strand nick, 5 – DNA ligase connects the two free ends of the nick.

and is illustrated in **Figure 4b**. Another type of DNA repair is DSB repair, which may involve homologous recombination or direct end rejoining. In homologous recombination (**Figure 5**), a damaged DNA strand is repaired using its homolog as a template (e.g., the maternal copy of a chromosome is used as a template if the paternal copy is damaged and vice versa). This process involves removal of damaged nucleotides and synthesis of new DNA. Homologous recombination may also be used to repair some DNA–DNA cross-links and some SSBs. Other cross-links are repaired in a process that combines aspects of homologous recombination and nucleotide excision repair. In end joining, the damaged bases at the ends of the break are removed and the broken ends are directly joined. Because no template is used to ensure

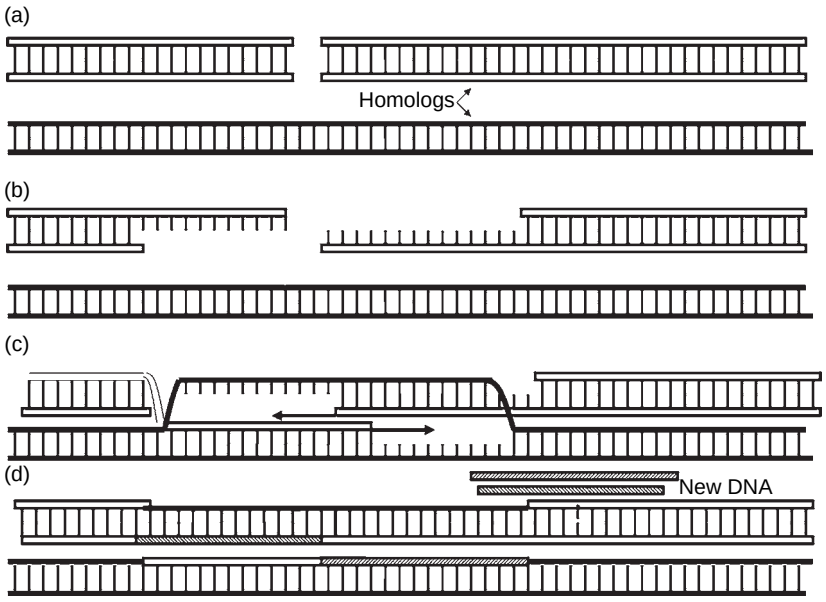

Figure 5 Homologous recombination repair of DNA DSB. (a) Damaged and undamaged homologs pair up; (b) damaged sections are removed by nucleases; (c) damaged and undamaged homologs cross over, polymerases use undamaged homolog to synthesize new DNA in damaged homolog; (d) DNA is cut at crossovers and ligated.

correct synthesis of new DNA, this may result in loss or changes in DNA sequence.

Mutations

Types of Mutations

DNA damage can result in a variety of mutations, including point mutations, frameshift mutations, and chromosomal mutations. Point mutations include changes in DNA sequence due to substitution of one base for another during DNA replication. For example, the DNA sequence AATTCGCATTG could be replicated as AAC̲TCGCC̲TTG. Changes in DNA sequence may or may not result in changes in amino acid sequence when the mutated DNA is used to code for protein. When DNA is translated into proteins, every three nucleotide bases (a 'codon') code for one amino acid. However, many amino acids are coded for by more than one codon. Thus, if a mutation occurs such that the mutated sequence codes for the same amino acid sequence as the old sequence, this is called a silent mutation. In evolutionary terms, this is also referred to as a neutral mutation. Silent (or neutral) mutations may also occur if there is a change in the amino acid sequence, but this does not alter the structure of the protein. However, if a point mutation results in a change in the structure or function of the protein, a nonfunctional, dysfunctional protein or a protein with impaired function could result. This is called a missense mutation. In addition, in a coding sequence of a gene, there are start codons and stop codons – locations that determine where the translation of the protein will begin and end on the mRNA molecule. If a mutation results in a premature stop codon, this will result in a truncated protein. This is known as a nonsense mutation, because the protein coded for by the mutated DNA is entirely nonfunctional. Another change in DNA sequence occurs if nucleotides are added or subtracted from the coding region. This is called a frameshift mutation, because it changes the reading frame and leads to a complete change in the amino acid sequence coded by the DNA.

Chromosomal mutations (also known as cytogenetic mutations) are changes in the structure or number of chromosomes. Chromosomal mutations are alternatively called chromosomal aberrations, chromosomal rearrangements, cytogenetic effects, cytogenetic aberrations, or clastogenic effects. The process of producing such effects is referred to as clastogenesis. Chromosomes can be visualized when they condense during mitosis or meiosis, and can be stained with various dyes. Because some regions stain darker than others, this produces a banding pattern when the chromosome is observed under a microscope. An unreplicated chromosome with a representative banding pattern is schematically illustrated in **Figure 6a**. The circle at the center represents the centromere: the place where the mitotic spindle attaches during cell division. The numbers refer to various positions on the undamaged chromosome. A DSB may lead to a break in the chromosome, as illustrated in **Figure 6b**.

If this break is unrepaired, it may lead to loss of a portion of the chromosome, called a deletion. If a piece of chromosome is deleted from the end, as illustrated in **Figure 6c**, this is called a terminal deletion. If there are

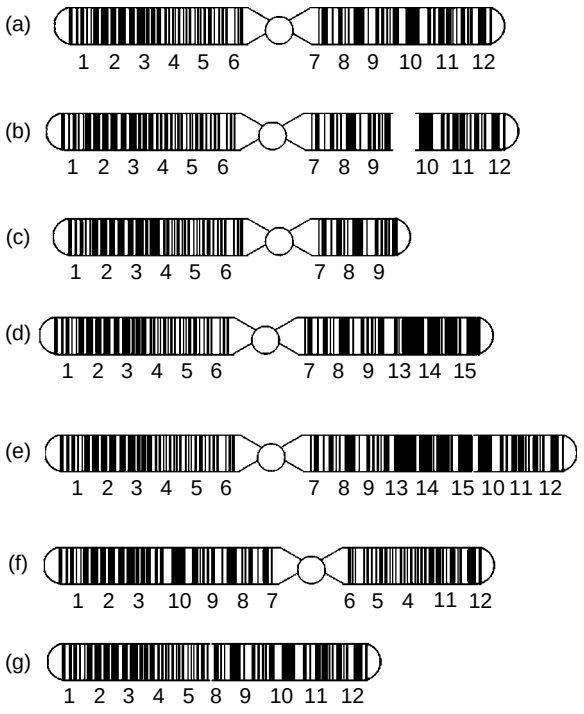

Figure 6 Diagram of possible chromosomal mutations. (a) Undamaged chromosome; (b) chromosome with break, (c) terminal deletion of positions 10–12; (d) translocation of a section containing positions 13–15 from another chromosome, (e) insertion of section 13–15 in between positions 9 and 10; (f) inversion of section from positions 4–10; (g) internal deletion of section 6–7, which contains the centromere.

breaks in two different chromosomes, they may exchange the ends distal to the breaks, a process known as translocation (**Figure 6d**). In some cases, a piece of a chromosome may be inserted in the interior of a different chromosome, a process known as insertion (**Figure 6e**). If there are two or more breaks in the same chromosome, a number of things can also happen. For example, an inversion may take place, where the piece of chromosome between the two breaks is 'flipped' (**Figure 6f**; this takes place between positions 4 and 10). Such double breaks may also result in an internal deletion. As illustrated in **Figure 6g**, if the breaks are on either side of the centromere, this may result in an acentromeric chromosome (a chromosome without a centromere). This could result in loss of an entire chromosome during cell division. The loss of an entire chromosome is called aneuploidy. Unfortunately, once formed, there is no way for a cell to repair chromosomal mutations.

Formation of Mutations

Spontaneous mutations

Mutations can be formed either endogenously or as a consequence of exposure to mutagenic agents. One type of endogenous mutations is spontaneous mutations, which may occur as a result of errors during DNA replication, for example, when a G is paired with a T instead of a C. This results in a mismatch. There are several types of enzymes, called mismatch repair enzymes, which can correct such mistakes. However, sometimes this mistake is not repaired and this results in a mutation. Strand breaks and abasic sites can also form spontaneously, for example, due to thermal energy arising from the heat produced by cellular metabolism or due to the inherent instability in the chemical bonds. Other types of spontaneous DNA damage include loss of amino groups on the bases or rearrangements in the chemical structure within the bases. Finally, endogenous mutations may occur as a result of endogenous DNA damage caused by ROSs formed by routine oxidative metabolism. Spontaneous and endogenous DNA damage may lead to mutations in mechanisms similar to mutagen-induced DNA damage, as discussed below.

Chemically induced mutations

Although they occur naturally, the occurrence of spontaneous mutations may be accelerated by chemical exposure. For example, the more rapidly a cell divides the greater the chance of a spontaneous mutation. Some chemicals increase the rate of cell division in some tissues (this is called cell proliferation), and thus the probability that a spontaneous mutation will occur. In addition, inhibition of DNA repair by arsenic, cadmium, or other metals may lead to increased incidence of spontaneous mutations, because of the reduced rate of removal of mismatches and endogenous DNA damage. Also, exposure to genotoxic agents may lead to mutations in the mismatch repair or other repair genes, leading to decreased rates of repair.

Mutations can also be induced by exposure to mutagenic compounds, which certainly applies to point mutations. Point mutations can be induced when damaged DNA is repaired or undergoes replication. DNA repair can lead to mutations because most types of DNA repair require DNA synthesis as an essential step, and the DNA polymerases involved in DNA repair are more prone to make errors than the polymerases involved in replicative DNA synthesis (S phase synthesis). The polymerases involved in homologous recombination are also more error-prone than those involved in DNA replication. During replication, DNA polymerases may also make a mistake if there is a damaged base. Such damaged bases may 'miscode'; for example, an A may be inserted instead of a C opposite an oxidized G, and a T may be inserted opposite a methylated G during DNA synthesis. If the replication enzymes encounter an abasic site, there is no information to determine which nucleotide should be inserted, so A's are inserted preferentially opposite an abasic site. If the replication enzymes encounter a bulky

lesion, replication may be arrested, and a new set of enzymes may be recruited to carry out translesion synthesis. In this type of synthesis, DNA is replicated past the lesion by so-called error-prone polymerases. These polymerases may induce a mutation because (1) the damaged bases may miscode, for example, an A may be inserted instead of a C opposite an adducted G, or (2) these polymerases are inherently error-prone, so they may make a mistake even at a site where there is no damage. Similar events may occur to produce frameshift mutations.

Frameshift mutations may occur in one of two ways. The first method involves replication of damaged bases. Deletion of one or more damaged bases (**Figure 7a**) may occur if there is a sequence with two or more of the same bases side by side, in this case two G's, one of which is damaged. During synthesis, the damaged G may 'bulge out' of the DNA strand, and the C on the opposite strand may then bind with the next, undamaged, G (**Figure 7a**). When DNA replication resumes, the new strand has a one-base deletion. Alternatively, if a DNA strand with a damaged G is replicated, a C may be inserted opposite the damaged G, but then it may be displaced by an A (some chemically modified G's may bind with A just as well as, or even better than, C). In this case, the C may bulge out, resulting in the newly synthesized strand having an extra base inserted. A second method of frameshift mutations may occur as a result of intercolating agents. These are chemicals that can intercolate or 'slip' between DNA bases, and may mimic a DNA base during DNA replication. represents a damaged guanine. Dotted line represents newly synthesized DNA.

Chromosomal mutations may occur as a result of DSBs. If such breaks are unrepaired, this may result in chromosomal deletions. Errors in repair of DSBs may lead to inversions, translocations, or insertions.

Finally, some organisms may undergo a phenomenon known as adaptive mutagenesis. In this process, environmental stressors cause an increase in endogenous or spontaneous mutations, presumably by endogenous inhibition of repair and mismatch detection. This is thought to be an adaptive mechanism whereby bacteria create *de novo* genetic variation, because some of the new variants may survive the stress better than others. It is not known if adaptive mutation occurs in eukaryotes, or genotoxic stressors can also induce adaptive mutations. However, a similar process occurs in cancer cells, which gradually accumulate more and more mutations after initiation of the tumor – a process called genomic instability. Latent genomic instability can also occur in radiation-exposed cells, which may spontaneously develop high numbers of mutations long after radiation exposure and initial repair of the damage to DNA.

Modulators of Mutagenesis

There are variety of endogenous and environmental factors that can modulate genotoxic responses and mutagenesis. For example, in some species, development

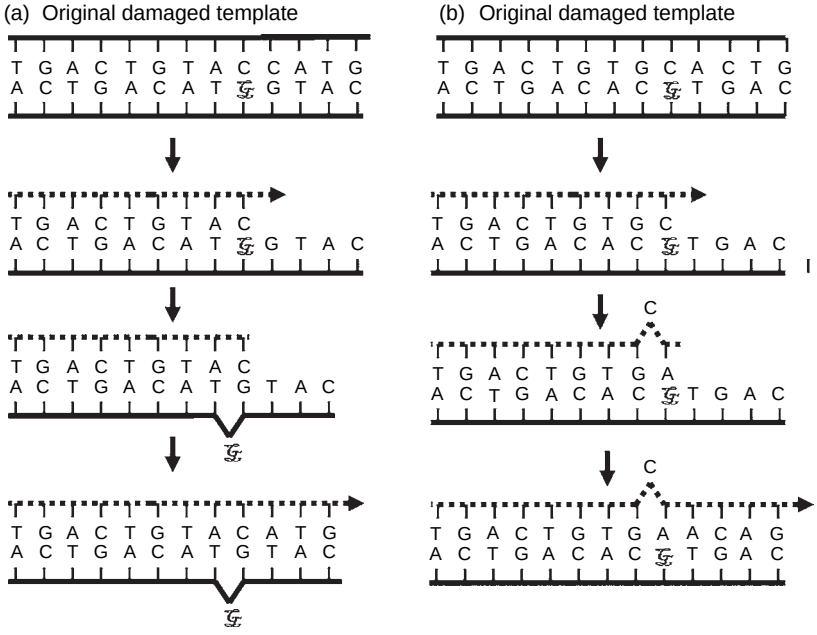

Figure 7 Hypothetical mechanisms for DNA damage-induced frameshift mutation formation. (a) Deletion in newly synthesized DNA; (b) insertion in newly synthesized DNA.

of neoplasia ('cancer') is sex dependent, so that mutagenesis is perhaps modulated by estrogen or other hormones. Because cell division in embryonic, larval, and juvenile organisms is more rapid than in adults, the adults may be less susceptible to such damage. Also, persistent DNA lesions (mutations or chromosomal abnormalities) may accumulate over time, so that older individuals are more likely to exhibit neoplasia or other mutagenic effects. Additionally, variation between individuals may be due to different exposure histories or genetic variability in cellular uptake, excretion, xenobiotic metabolism, or DNA repair. Environmental factors that modulate DNA damage and mutagenesis include temperature (which may mediate carcinogen metabolism or DNA repair rates in these ectotherms), dissolved oxygen concentration in water (which may mediate oxidative stress), salinity or ionic composition of water, or food availability and chemical composition. Also, the amount of DNA damage in fish may vary with season, perhaps due to temperature or bioenergetic or hormonal status. Furthermore, concomitant exposure to other chemicals may promote DNA damage or promote mutagenesis. Thus, the amount of DNA damage induced by complex mixtures may be much more than that predicted by single-chemical genotoxic effects. Finally the degree of genotoxic or mutagenic effects may be mediated by intra- and interspecific interactions such as competition, predation, parasitism, trophic structure and complexity of the ecosystem, and population density of affected organisms.

Effects on Fitness and Ecological Parameters

Environmentally induced DNA damage and resultant mutations may be pertinent for ecologically relevant organisms because they may affect organismal-level fitness components. This may be translated into effects on populations, and eventually communities and ecosystems. This is illustrated in **Figure 8**. First, because DNA damage and mutations can lead to cell death and cancer, this may affect survival. Because DNA damage enhances the rate of cell senescence, accumulation of unrepaired damage and mutations may affect longevity and population age structure. DNA damage and mutations have their greatest deleterious effect on rapidly dividing cells. Because gonadal germ cells are rapidly dividing, they are particularly susceptible to the effects of DNA damage and mutations. Growth may also be affected because of induced cell death, interference with DNA replication, or induced delay of cell division (DNA damage induces cell cycle delay, a phenomenon that halts the cell cycle to allow time for repair before DNA replication or mitosis). Immune cells, both mature white blood cells and white blood cell stem cells (which divide rapidly), are also particularly susceptible to the effects of genotoxins and mutagens. An inhibited immune system may in turn affect fitness of affected organisms. Genotoxic effects may also affect bioenergetics or organisms for two reasons. First, DNA repair is an energetically expensive process. Second, mitochondria contain their own DNA, and damage and mutations in mitochondrial genes may affect mitochondrial function and ATP production. Furthermore, DNA damage and mutagenesis may affect development, both by inducing teratogenic (causing developmental defects) mutations and by delaying development because of cell cycle delay and interference with DNA replication. Finally, DNA damage in nerve cells may result in acute neurological effects, neurodegeneration, or neurodevelopmental effects.

Mutations in germ cells may result in heritable mutations that can be passed on to future generations (transgenerational effects) or can spread through the

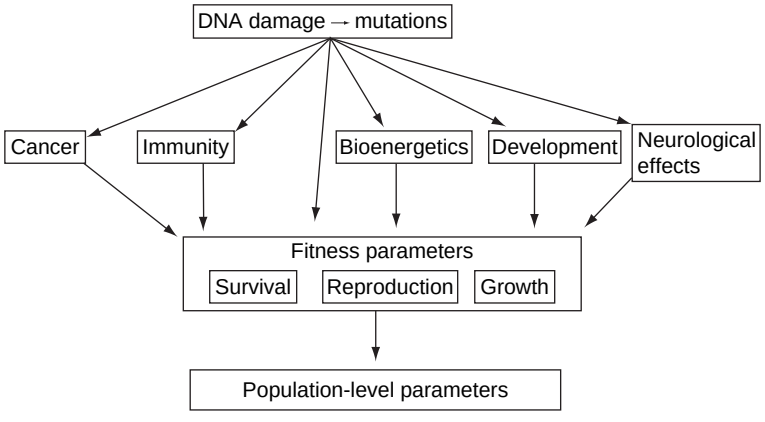

Figure 8 Possible mechanisms whereby DNA damage and/or mutations may affect fitness of organisms.

populations. Spontaneous and endogenous germ-line mutations are relevant in evolutionary terms. Missense, nonsense, and frameshift mutations are almost always harmful, or deleterious, but in some rare instances may produce a phenotype with an adaptive advantage (beneficial mutations) in certain environments. Chromosomal mutations are mostly deleterious (especially aneuploidy), although some may be neutral, and a few may provide an adaptive advantage. If they do provide such an advantage, they may increase in frequency in the population due to natural selection. If dominant mutations in germ cells (i.e., gamete stem cells) result in the death of the offspring, these are called dominant lethal mutations. Deleterious mutations may eventually be removed from the population, but this may take many generations, especially if they are only mildly deleterious. If the deleterious mutation is recessive rather than dominant, it may persist indefinitely in the population. Neutral, beneficial, recessive, and mildly deleterious mutations may persist in the populations and increase population genetic diversity over time.

Environmentally induced mutations (i.e., due to chemical exposure, ionizing radiation, or UV) can affect survival, metabolism, growth, reproduction, propensity to develop cancer, or behavior in offspring or other descendants at any life stage. If these mutations are expressed in a dominant fashion, their effects may be always apparent when a mutant allele is present. If they are recessive mutations, the mutant phenotype is apparent only in the homozygous state. Exposure to mutagenic agents may increase the mutation rate of populations, that is, the number of new mutations per generation.

The relative number of persistent deleterious mutations in the population is called the mutational load. The deleterious effects of mutational load may depend on population size, because smaller populations have a higher level of inbreeding (the mating of genetically similar individuals). This leads to increased number of homozygous loci in the population, which increases the chance that deleterious recessive mutations are expressed – a process known as inbreeding depression. Small populations may experience inbreeding depression, which leads to further reduction in population size due to decreased average fitness, which leads to further inbreeding depression, etc., such that these populations may spiral toward extinction in a phenomenon called mutational meltdown. Exposure to mutagenic agents may hasten this process. Thus, although exposure to mutagenic contaminants may increase population genetic diversity and thus hasten the rate of evolution, loss of fitness may also result in population bottlenecks and reduction of genetic diversity. If the relative loss of fitness is genotype dependent, this may lead to evolution of more mutagen-resistant populations.

See also: Air Quality Modeling; Evolutionary Ecology: Overview; Fitness; Pollution Indices; Population and Community Interactions; Radiation Balance and Solar Radiation Spectrum.

Further Reading

Loechler EL (1996) The role of adduct site-specific mutagenesis in understanding how carcinogen–DNA adducts cause mutations: Perspective, prospects and problems. *Carcinogenesis* 17: 895–902.

Norbury CJ and Hickson ID (2001) Cellular responses to DNA damage. *Annual Reviews of Pharmacology and Toxicology* 41: 367–401.

Rosenberg SM (2001) Evolving responsively: Adaptive mutation. *Nature Reviews Genetics* 2: 504–515.

Sarasin A (2003) An overview of the mechanisms of mutagenesis and carcinogenesis. *Mutation Research* 544: 99–106.

Shugart LR, Theodorakis CW, Bickham AM, and Bickham J (2002) Genetic effects of contaminant exposure and potential impacts on animal populations. In: Calow P (ed.) *Handbook of Ecotoxicology*, pp. 1129–1148. Oxford: Blackwell Science.

Wang Z (2001) DNA damage-induced mutagenesis: A novel target for cancer prevention. *Molecular Interventions* 1: 269–281.

Wirgin I and Theodorakis CW (2002) Molecular biomarkers in aquatic organisms: DNA- and RNA-based endpoints. In: Adams SM (ed.) *Biological Indicators of Aquatic Ecosystem Health*, pp. 73–82. New York: American Fisheries Society.