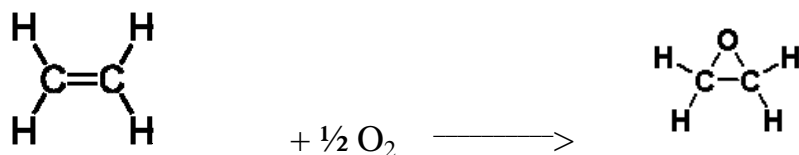


### 3.15 FORMATION OF EPOXIDES AND CARCINOGENIC PRODUCTS

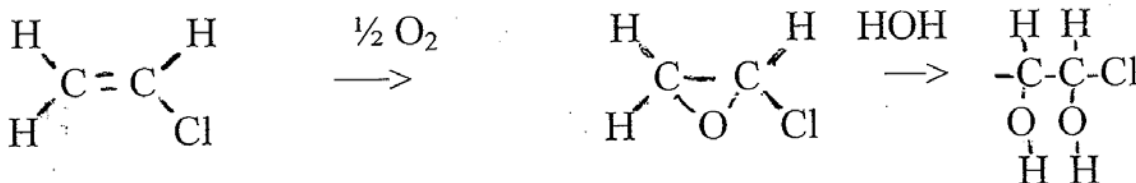
**Ethylene oxide** is made by treating ethylene ( $C_2H_4$ ) with a limited supply of  $O_2$  to make  $C_2H_4O$ , the basic epoxide molecule.



Ethylene oxide

It is unstable for the same reasons that cyclopropane: a huge bond angle strain. It has been used as a sterilizer for plastic medical equipment such as endoscopes which cannot withstand the high temperatures of an autoclave. The extremely reactive **epoxide ring** reacts and oxidizes and destroys most of the molecules in any biological organism or virus. It is however extremely toxic, potentially explosive as well as carcinogenic and requires very strict procedures and careful monitoring.

**Vinyl chloride epoxide.** Vinyl chloride is the monomer used to make the very common plastic, polyvinylchloride (PVC). In the body vinyl chloride can undergo metabolism in the liver to form reactive and potentially mutagenic vinyl chloride epoxide.



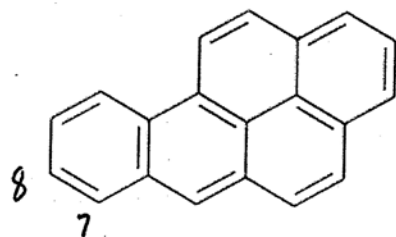
Ideally the epoxide will then react with a water molecule to form a diol (a molecule with 2 alcohol functional groups) and be excreted in the urine. But the reactive epoxide group also has the potential for reacting with DNA and causing a mutation.

Exposure to vinyl chloride produces intoxication similar to that of ethanol. Long term exposure (i.e. workers in vinyl chloride manufacturing plants) is associated in particular with liver angiosarcoma, which is normally a very rare type of cancer. Human exposure to vinyl chloride is very strictly controlled in factories making polyvinylchloride (PVC). PVC itself is not a carcinogen because the reactive double bonds are removed in the process of making the PVC polymer.

**Benzopyrene** (sometimes jokingly referred to as 2,4,6,8 “chickenwire”) is a carcinogen found in smoked and charred materials: cigarette smoke, marijuana smoke, wood smoke, and lesser amounts in char-broiled steaks. It appears to be the primary molecule responsible for the carcinogenic properties of tobacco smoke. (Even before cigarette smoking became popular in the early twentieth century, smoke was suspected as a carcinogen. A London surgeon, Percival Potts first noted in 1775 that young chimney sweeps were at increased risk of cancer of the scrotum (call “soot warts”).

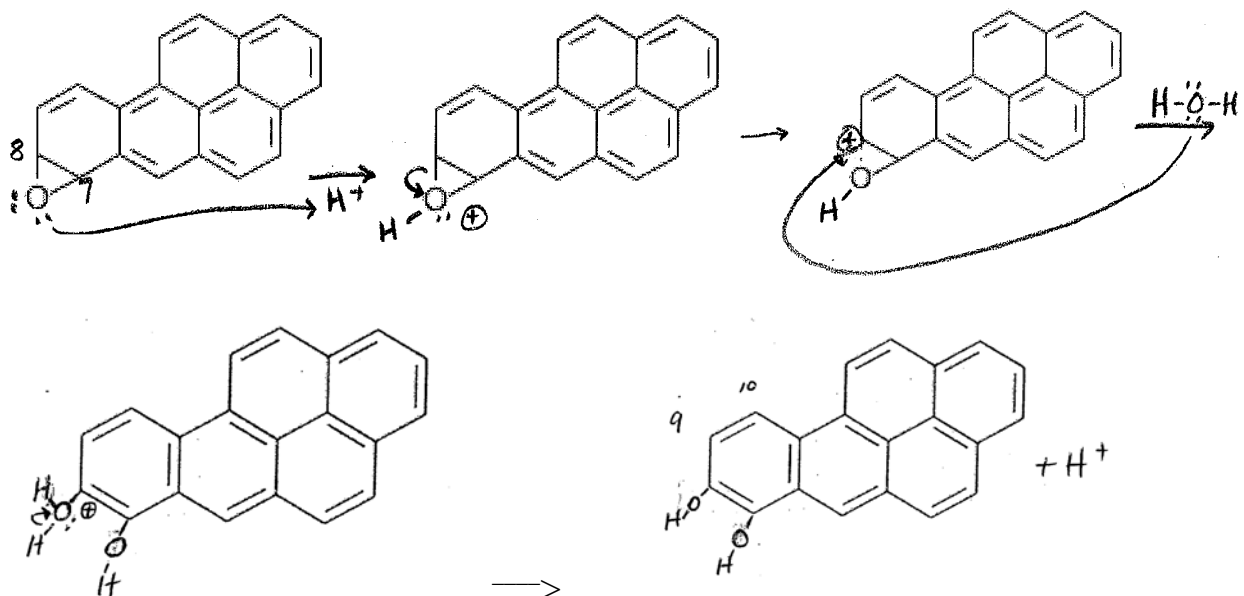


Later the chimney sweeps guild in Denmark recommended that chimney sweeps take daily baths and this resulted in decreased incidence of this form of cancer, at least in Denmark according to a study published in the British Medical Journal in 1892. It should be noted that daily baths were not a routine activity in 19<sup>th</sup> century Europe!)

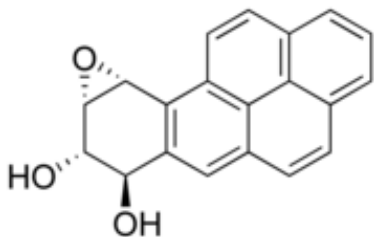


When a person breathes or absorbs benzopyrene, the benzopyrene cannot be utilized in the body and the body seeks to dispose of it. The primary route of excretion for unwanted substances in the body is to excrete them in the urine or feces. This requires that the substance be water soluble. The structure of

benzopyrene is completely non-polar so it is not soluble in urine. The body's liver seeks to make it more water soluble by adding polar OH groups. The liver has a whole family of enzymes called the **cytochrome P-450** family, which adds polar groups (often OH) to molecules to increase their water solubility and prepare them for excretion. In the reaction pathway for benzopyrene an O atom is first added to the 7,8 position (see structure) creating an unstable intermediate, benzopyrene 7,8 epoxide. The O atom on the unstable 3-membered ring can pick up a hydrogen ion, followed by attack by a pair of electrons on the O of a water molecule as shown below.

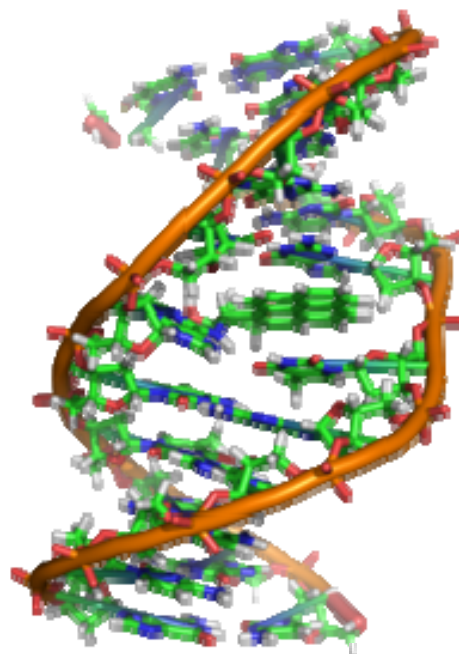
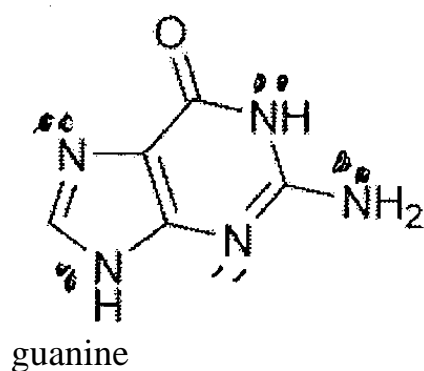


Adding a water molecule produces benzopyrene 7,8 dihydrodiol. A second epoxide is then added across the #9 and 10 C atoms to make benzopyrene 7,8 dihydrodiol 9,10 epoxide.



The second epoxide molecule may react with glucuronic acid (remember bilirubin metabolism!) or adds another water molecule. In either case the additional OH groups will result in increased water solubility and excretion in urine. This is all well and good, and exactly what Mother Nature intended. Unfortunately the “best laid plans of mice and men oft’ go awry” to quote the Scottish poet Robert Burns.

The benzopyrene epoxide molecule has a tendency to slip in between the **purine** and **pyrimidine** bases in the DNA double helix, a process called **intercalation**. It reacts readily with available pairs of electrons on the DNA bases. It appears to have a preference for reacting with the amine group on guanine bases. (Can you guess what parts of the guanine might be most reactive?) This reaction will cause a mutation in the DNA.



This mutation will most likely be found by DNA repair enzymes and be repaired, but there is a small chance that it will not. The mutation may have different results depending on the exact location in the DNA.

Some of the many possibilities:

- 1) The mutation may occur in a portion of DNA that isn't critically important and produce no result.
- 2) The mutation may occur in a portion of DNA that is absolutely essential to the cell's health and cause the cell's death.

3) The mutation may occur in a portion of DNA that controls cell replication. As a result it may produce a cell that starts replicating and the replication cannot be “shut off”. In this case the mutation has started the formation of a tumor. (There is some evidence that benzopyrene epoxide preferentially **intercalates** into a portion of the DNA for a gene called P53, which controls the cell replication cycle.)