Introduction

Psoralens (furocoumarins) of natural or synthetic origin show photosensitizing activity on biological systems in the presence of long-wave ultraviolet radiation (320-400 nm) (UVA) (Musajo and Rodighiero 1972, Scott et al. 1976, Ben-Hur and Song 1984, Hearst et al. 1984). Photosensitization by psoralens is believed to be mainly due to a photomediated covalent binding to pyrimidine bases in DNA. The DNA photobinding involves the following steps: formation of psoralen-DNA complexes in the dark and, in the presence of UVA, induction of monoadducts and diadducts (DNA interstrand cross-links). Mono-functional furocoumarins photoinduce only monoadducts, bifunctional furocoumarins mono- and diadducts (Ben-Hur and Song 1984).

The mutagenicity of psoralens has been studied for mainly two reasons: 1. Bifunctional psoralens such as 8-methoxypsoralen (8-MOP), 5-methoxypsoralen (5-MOP) and \(4',5',8\)-trimethylpsoralen (TMP) are widely used in the photochemotherapy (PUVA) of psoriasis and other skin diseases, and some of them are present in cosmetics including skin tanning preparations (Ben-Hur and Song 1984). The frequent or prolonged utilisation of psoralens raises the question on their genotoxic (mutagenic and carcinogenic) potential. (IARC 1986). 2. In the photoreaction of psoralens cellular DNA is one of the major targets. Psoralens photoinduce well-defined lesions, i.e. pyrone-side and furan-side monoadducts and, in the case of bifunctional derivatives, DNA interstrand cross-links (Musajo and Rodighiero 1972, Hearst et al. 1984). These adducts are relatively stable through DNA extracting procedures. Thus, it is possible to study the induction of specific lesions, their repair and the mutagenic consequences in cells after treatment with psoralens and UVA. Such studies are useful not only for fundamental research but also for selecting new psoralens for photochemotherapeutic use.

Psoralen induced lesions, when left unrepaired, may represent obstacles which effectively inhibit the progression of the replication fork in living cells.
The resulting antiproliferative effects are thought to be particularly relevant in the photochemotherapeutic treatment of psoriasis (Anderson and Voorhees 1980). The inhibition of DNA synthesis can be overcome by repair or translesional synthesis (bypass) (Smith 1987). Different enzymatic steps are known to be involved in this repair which may or may not be error-prone and mutagenic. The processing of furocoumarin plus UVA induced lesions has been reviewed in great detail (Smith 1987).

In earlier work (Cole 1971, Ben-Hur and Elkind 1973), psoralen plus UVA induced monoadducts were considered more easily repairable than photoinduced DNA cross-links. However, recent studies indicate that the reparability of monoadducts depends very much on their structure and distribution in DNA. The repair of psoralen induced damage in repair competent cells necessitates the action of gene products which are also involved in the repair of UV-induced pyrimidine dimers and other bulky lesions. The repair of DNA cross-links may involve a sequential action of several repair pathways (see for review, Smith 1987, Moustacchi 1987).

Psoralens have been found to be photomutagenic in all pro-and eukaryotic cell systems tested. Valuable information has been gained from tests in bacteria, however, because of the more complex organisation (chromosomal and chromatin structure) and the presence of different repair systems in eukaryotes are important.

The present review will focus on psoralen derivatives of photochemotherapeutic interest, i.e. bifunctional furocoumarins (8-MOP, 5-MOP and TMP) in phototherapeutic use (Fitzpatrick and Pathak 1984, Wolff and Hönigsmann 1984) and newly developed monofunctional derivatives, methylated angelicins (Rodighiero et al. 1987) and 3-carbethoxypsoralen (3-CPs) (Queval and Bisogni 1974) and the pyridopsoralens 7-methyl pyrido (3,4-c)psoralen (MePyPs) and pyrido-(3,4-c)psoralen (PyPs) (Moron et al. 1983). The eukaryotic cell systems include yeast and mammalian cells in culture. It is shown that the mutagenicity of psoralens depends on psoralen structure and functionality (mono vs bifunctional), activating wavelengths, dose (fluence) rate and the presence and absence of oxygen.

Comparisons of photobiological activities of psoralens at equal concentration and UVA doses appear to be useful for photochemotherapeutic considerations, as are comparisons at equal survival levels for genotoxic (mutagenic) effects. However, psoralen derivatives differ in their dark complexing, their light absorption characteristics and their photoreactivity (towards DNA). Thus, comparisons at equal number of photoadducts induced are more suitable for