Ratan Singh Ray · Chandana Haldar
Ashish Dwivedi · Neeraj Agarwal
Jyoti Singh *Editors*

Photocarcinogenesis & Photoprotection

Springer

Photocarcinogenesis & Photoprotection

Ratan Singh Ray
Chandana Haldar • Ashish Dwivedi
Neeraj Agarwal • Jyoti Singh
Editors

Photocarcinogenesis & Photoprotection

Springer

Editors
Ratan Singh Ray
Indian Institute of Toxicology Research
Lucknow, Uttar Pradesh, India

Ashish Dwivedi
Department of Zoology
Banaras Hindu University
Varanasi, Uttar Pradesh, India

Jyoti Singh
Photobiology Division
Indian Institute of Toxicology Research
Lucknow, Uttar Pradesh, India

Chandana Haldar
Department of Zoology
Banaras Hindu University
Varanasi, Uttar Pradesh, India

Neeraj Agarwal
Anschutz Medical Campus
University of Colorado Denver
Aurora, CO, USA

ISBN 978-981-10-5492-1 ISBN 978-981-10-5493-8 (eBook)
https://doi.org/10.1007/978-981-10-5493-8

Library of Congress Control Number: 2018959229

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd.
The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

Preface

It is our privilege and honor to write the first edition of book on unique subject of *Photocarcinogenesis and Photoprotection*.

Incidences of skin cancer are increasing globally which is caused mainly by repeated and increased exposure to ultraviolet or sunlight through increased outdoor activities, changes in clothing style, increased longevity, ozone depletion, genetics and immune suppression. This prompt us to educate others by putting together information on ultraviolet radiation exposure, how it initiates cancer, mechanisms involved, potential therapy, and what protective measures can be taken. This book also covers how commonly used therapeutic drugs, personal care products, and other chemicals when consumed or applied to the body can be toxic under exposure to UV radiation.

Although there is an increasing awareness about harmful effects of UV radiation, exposure to UVR is still unavoidable, and people need to be educated on how UV radiation causes its harmful effects and what protective measures can be taken.

All the authors in this book are highly skilled researchers with thorough and up-to-date knowledge in the field and are actively doing research in the relevant fields. For all the chapters, we put our best efforts to provide collated information from research articles published so far related to the subject and arranged them in subsections to make them easy to follow. We have tried our best to use the simplified language so that it can be understandable to all levels of readers.

We hope that after reading the book, the reader will have more knowledge, understanding, and awareness about the harmful effects of repetitive or chronic UV radiation exposure as well as its interactions with other chemicals and drugs on the skin or inside the body.

Lucknow, Uttar Pradesh, India — Ratan Singh Ray
Varanasi, Uttar Pradesh, India — Chandana Haldar
Varanasi, Uttar Pradesh, India — Ashish Dwivedi
Aurora, CO, USA — Neeraj Agarwal
Lucknow, Uttar Pradesh, India — Jyoti Singh

Acknowledgments

I am heartily thankful to all the authors for investing time and efforts in writing the chapters for the book. I highly appreciate that they took extra stress besides their other commitments to provide detailed information based on their experience and from literature to make all the chapters in this book entitled *Photocarcinogenesis and Photoprotection* up-to-date and more valuable for its readers. We also like to take this opportunity to convey our special thanks to Prof. Alok Dhawan, Director of CSIR-IITR, Lucknow, for his support, guidance, and valuable suggestions throughout the preparation of this new edition.

Contents

Contributors

Neeraj Agarwal Urology Division, Department of Surgery, Anschutz Medical Campus, University of Colorado Denver, Aurora, CO, USA

Shikha Agnihotry Department of Biomedical-informatics, Sanjay Gandhi Post Graduate Institute, Lucknow, India

Saroj K. Amar Department of Forensic Science, School of Bioengineering and Biosciences, Lovely Professional University, Phagwara, Punjab, India

Mohammad Anas Photobiology Division, CSIR-Indian Institute of Toxicology Research, Lucknow, Uttar Pradesh, India

Monisha Banerjee Molecular and Human Genetics Laboratory, Department of Zoology, University of Lucknow, Lucknow, Uttar Pradesh, India

Deepti Chopra Photobiology Laboratory, Systems Toxicology and Health Risk Assessment Group, CSIR-Indian Institute of Toxicology Research, Lucknow, Uttar Pradesh, India

Babu Banarasi Das University, Lucknow, Uttar Pradesh, India

Divya Dubey Photobiology Laboratory, System Toxicology and Health Risk Assessment Group, CSIR- Indian Institute of Toxicology Research, Lucknow, Uttar Pradesh, India

Babu Banarasi Das University, Lucknow, India

Ashish Dwivedi Pineal Research Lab, Department of Zoology, Institute of Science, Banaras Hindu University, Varanasi, Uttar Pradesh, India

Shruti Goyal Photobiology Laboratory, System Toxicology and Health Risk Assessment Group, CSIR- Indian Institute of Toxicology Research (IITR), Lucknow, Uttar Pradesh, India

Kailash Chand Gupta CSIR-Institute of Genomics and Integrative Biology, Delhi, India

Department of Biological Sciences and Bioengineering (BSBE) and Centre for Environmental Science and Engineering (CESE), Indian Institute of Technology, Kanpur, India

Syed Faiz Mujtaba Department of Zoology, Faculty of Science, Shia P.G. College, University of Lucknow, Lucknow, Uttar Pradesh, India

Sandeep Negi Photobiology Laboratory, System Toxicology and Health Risk Assessment Group, CSIR- Indian Institute of Toxicology Research (IITR), Lucknow, Uttar Pradesh, India

Manish Kumar Pal Department of Obstetrics and Gynecology, King George's Medical University, Lucknow, Uttar Pradesh, India

Lipika Ray Pharmaceutics and Pharmacokinetics Division, CSIR-Central Drug Research Institute, Lucknow, Uttar Pradesh, India

Ratan Singh Ray Photobiology Division, CSIR- Indian Institute of Toxicology Research (IITR), Lucknow, Uttar Pradesh, India

Department of Zoology, Faculty of Science, Shia P.G. College, Lucknow, India

CSIR-Institute of Genomics and Integrative Biology, Delhi, India

Department of Biological Sciences and Bioengineering (BSBE) and Centre for Environmental Science and Engineering (CESE), Indian Institute of Technology, Kanpur, India

Jyoti Singh Photobiology Laboratory, Systems Toxicology and Health Risk Assessments Group, Indian Institute of Toxicology Research, Lucknow, Uttar Pradesh, India

Academy of Scientific and Innovative Research, New Delhi, India

Ajeet Kumar Srivastav Photobiology Division, System Toxicology and Health Risk Assessment Group, CSIR-Indian Institute of Toxicology Research, Lucknow, Uttar Pradesh, India

Babu Banarasi Das University, Lucknow, India

Amit Kumar Tripathi Electrophysiology Lab, School of Biomedical Engineering, IIT (BHU), Varanasi, Uttar Pradesh, India

Jaya Upadhayay Babu Banarasi Das University, Lucknow, India

Ankit Verma Photobiology Laboratory, System Toxicology and Health Risk Assessment Group, CSIR- Indian Institute of Toxicology Research (IITR), Lucknow, Uttar Pradesh, India

Neera Yadav Molecular and Human Genetics Laboratory, Department of Zoology, University of Lucknow, Lucknow, Uttar Pradesh, India

About the Editors

Prof. Ratan Singh Ray is a Senior Principal Scientist and Head of Photobiology Division, CSIR-Indian Institute of Toxicology Research, Lucknow. He is also serving as a Professor in AcSIR, CSIR. He had joined CSIR-IITR in 1991 as a Scientist. He has 26 years of research experience in the area of photosciences. Presently, he is working on photosafety issues of different nanomaterials used in personal care products and identifying novel nanotized phytochemicals for use in cosmetics, hair dyes, as well as sunscreen for photosafety against UVR. He is an active member of various scientific societies including the Bureau of Indian Standards (Cosmetics Sectional Committee PCD 19), India; American Society for Photobiology, USA; Indian Photobiology Society, India; and Society of Toxicology, India. He has published many research articles in reputed journals of *Photochemistry and Photobiology*, *Toxicology*, *Biomaterials*, *The Journal of Hazardous Materials*, etc.

Prof. Chandana Haldar is the Head of the Department of Zoology, Institute of Science, Banaras Hindu University, Varanasi, India. She has 30 years of research experience in photosciences. She has edited many books and published more than 200 research papers in the reputed journals of *Photosciences*. She has been twice awarded Alexander von Humboldt Fellowship of Germany to work on the steroid receptors and the pineal gland and immune function (1986–1987 and 1990–1991). Besides three decades of training, research, and teaching experience, she has also served as Chairperson and member of various societies, academic councils, and administrative bodies in and outside Banaras Hindu University.

Dr. Ashish Dwivedi is a Postdoctoral Scientist in the Pineal Research Lab, Department of Zoology, BHU, Varanasi. He has done his doctoral research from the Photobiology Division, Indian Institute of Toxicology Research (IITR), Lucknow. His doctoral research work was focused on phototoxicity assessment of different therapeutic drugs and environmental pollutants. He has 10 years of research experience in photosciences and published many papers in reputed journals of *Photochemistry and Photobiology*, *Toxicology*, *Biomaterials*, *The Journal of Hazardous Materials*, etc.

Dr. Neeraj Agarwal is working as a Research Instructor in NCI-designated University of Colorado Comprehensive Cancer Center, Aurora, CO, USA. Previously, he has completed his Ph.D. (2001 to 2007) in photobiology Division of Indian Institute of Toxicology Research (IITR), Lucknow. His work was focused on determining the phototoxic potential of commonly used therapeutic drugs and their mechanism of action. He has published seven research papers and presented his work at various conferences. He has received Best Poster Award in 2002 for the work related to ciprofloxacin phototoxicity. In 2007, he joined the Louisiana State University Health Sciences Center (LSUHSC), New Orleans, USA, as a Postdoctoral Researcher and worked for 5 years toward understating the role of MTBP protein in osteosarcoma metastasis and also on identifying and characterizing the cancer stem cells in osteosarcoma. He has received Scientific Excellence Award and was invited to present his work in the Cancer Center Retreat in 2010. Till now, he has published 18 research articles in reputed international journals with high impact factors, including *Cancer Research*, *Oncogene*, *Cell Death & Differentiation*, *Clinical Cancer Research*, and *Photochemistry and Photobiology*.

Jyoti Singh is presently pursuing her doctoral research from the CSIR-Indian Toxicology Research Institute, Lucknow, under the supervision of Dr. Ratan Singh Ray, Head of Photobiology Division. She did her master's degree in forensic science from Bundelkhand University, Jhansi. She is a member of the Indian Photobiology Society, India. She has published a book chapter and research papers in reputed journals like *The International Journal of Biochemistry & Cell Biology*, *Toxicology Letters*, *Biomaterials*, *The Journal of Hazardous Materials*, etc.

Abbreviations

UVR	Ultraviolet radiation
EMR	Electromagnetic radiations
MED	Minimal erythema dose
SED	Standard erythemal dose
MBD	Methyl-CpG-binding domain proteins
HDACs	Histone deacetylases
5mC	5-Methylcytosine
5hmC	5-Hydroxymethylcytosine
TDG	Thymine DNA glycosylase
PAs	Proanthocyanidins
GTP	Green tea polyphenols
EGCG	Epigallocatechin-3-gallate
α-MSH	α-Melanocyte-stimulating hormone
CREB	cAMP response element-binding protein
8-OHdG	8-Hydroxy-2'-deoxyguanosine
CPD	Cyclobutane pyrimidine dimers
NBCC	Nevoid basal-cell carcinoma
LC	Langerhans cells
CHS	Contact hypersensitivity
TLR	Toll-like receptor
ODS	Ozone depleting substances
FDA	Food and Drug Administration
MMPs	Matrix metalloproteinases
ECM	Extracellular matrix
NSAIDs	Nonsteroidal anti-inflammatory drugs
PAHs	Polycyclic aromatic hydrocarbons
IARC	International Agency for Research on Cancer
PDT	Photodynamic therapy

Ultraviolet Radiation (UVR): An Introduction

1

Ashish Dwivedi, Amit Kumar Tripathi, Jyoti Singh, and Manish Kumar Pal

Abstract

Radiant energy of sun is essential to perform metabolic processes of all flora and fauna on the earth. The electromagnetic radiations (EMR) emitted by sun extend from very long wavelength radiation, such as radiowaves (A ″′ 3×10^{8} m), to very short wavelength radiation, such as cosmic rays (A ″′ 3×10^{-19} m). The EMR reaching at the earth surface contains wavelength from 290 to 4000 nm. However, the UV portion covers from 200 to 400 nm. The range from 200 to 400 nm is often arbitrarily categorized into UVA, UVB, and UVC radiation. Solar radiation less than 290 nm does not reach at the earth's surface due to the presence of O_3 layer in stratospheric zone. But, last from few decades due to anthropogenic activities, the concentration of ozone layer decreases on stratospheric zone. As a consequence of that, UVB radiation levels are rising to 1% a year. Thus, the deleterious health effects on human beings (skin aging, cataracts, skin cancer, and immune suppression) are enhanced by UVR.

A. Dwivedi (✉)
Pineal Research Lab, Department of Zoology, Institute of Science, Banaras Hindu University, Varanasi, Uttar Pradesh, India

A. K. Tripathi
Electrophysiology Lab, School of Biomedical Engineering, IIT (BHU), Varanasi, Uttar Pradesh, India

J. Singh
Photobiology Laboratory, Systems Toxicology and Health Risk Assessments Group
CSIR-Indian Institute of Toxicology Research (CSIR-IITR), MG Marg, Lucknow, Uttar Pradesh, India

M. K. Pal
Department of Obstetrics and Gynecology, King George's Medical University, Lucknow, Uttar Pradesh, India

R. S. Ray et al. (eds.), *Photocarcinogenesis & Photoprotection*,
https://doi.org/10.1007/978-981-10-5493-8_1

Keywords
UVR · EMR · Ozone · Skin cancer · Skin aging

1.1 Introduction

Terrestrial life depends on radiant energy of sun which is essential for metabolic processes of all the living systems. Without sunlight, the surface of the earth would be cold and completely lifeless. From the beginning of life, light was an essential component of man's life. The word "radiation" originated from the Egyptian sun god "Atom Ra." It is depicted as the rays of the sun ending in hands holding the symbol of life. Sir Isaac Newton, in 1669, found that white light gets separated into different colors when passing through crude glass prism. Johann Wilhelm Ritter from Jena in Germany discovered UVR [1]. After 200 years of the discovery of UV rays, nobody would question the importance of Ritter's discovery and the consequences of it in photodermatology and photomedicine. In 1845, Bonnet used sunlight to treat tuberculosis arthritis [2]. Jewish physicians in Arabia recommended sunbaths for health.

Niels Finsen work established the branch of modern photobiology. He fixed the role of ultraviolet radiation (UVR) in sunburn [3]. Finsen is the pioneer of heliotherapy and actinotherapy throughout Europe and the USA. Saleeby in 1926 discussed the importance of heliotherapy and treatment of surgical tuberculosis by natural sunlight [4].

1.1.1 Electromagnetic Radiation (EMR)

The interaction of EMR with matter can be described by viewing it either as a continuous wave (wave description) or as a series of packets containing energy (particle description). Transmission through space, scattering, and diffraction can be understood using the wave description. EMR is a form of energy and can be characterized as a continuous wave of regular oscillations of electric and magnetic fields. These fields are perpendicular to each other and to the direction of propagation. However, the absorption of EMR by molecule and the photoelectric effect are best understood when the particle description of EMR is used. In the particle description, EMR is contained in discrete packets, called photons.

The energy of EMR is directly proportional to the frequency of the oscillation of the two fields:

$$E = \mathrm{h}\nu \tag{1.1}$$

where E = energy of a photon, h = Planck's constant (6.63×10^{-34} J.s), and ν = frequency.

The product of the frequency and the wavelength is equal to a constant, the speed of light in a vacuum:

$$v\lambda = c \tag{1.2}$$

where λ = wavelength and c = speed of light in vacuum.

Therefore, the energy of EMR is inversely proportional to its wavelength:

$$E = \frac{\mathrm{h}c}{\lambda} \tag{1.3}$$

The unit most often used for wavelength in the UV and visible range is the nanometer, which is 1×10^{-9} m. The EMR extends from very long wavelength radiation (low energy), such as radiowaves (A ″′ 3×10^{8} m), to a very short wavelength radiation (high energy), such as cosmic rays (A ″′ 3×10^{-19} m). The EMR reaching at the earth surface from the sun contains wavelength from 290 to 4000 nm. The radiation is described as UV, visible, or infrared, depending upon the wavelength. The UV portion of the EMR covers from 200 to 400 nm. Solar radiation shorter than 290 nm is absorbed by O_3 in the stratosphere and does not reach at the earth's surface. The range from 200 to 400 nm is often arbitrarily divided into UVA, UVB, and UVC radiation. It is based on skin reactions in human. The UVA portion (320–400 nm) is longer-wavelength UVR; it is not strongly absorbed by proteins and nucleic acids. It does not cause erythema in normal skin at moderate doses in the absence of photosensitizing chemicals. This range is also called black light and near-UVR. UVB radiation (290–320 nm) is erythemogenic and is present in the terrestrial solar spectrum. It is also referred as sunburn radiation and midrange UVR. UVC radiation (200–290 nm) is biologically active but does not reach at the earth's surface. However, the 254 nm wavelength in low-pressure mercury lamps (germicidal lamps) is frequently used in experiments as a source of UVR.

The spectral distribution of solar irradiance, as measured above the earth's surface, is the infrared (>760 nm) and visible regions accounting for the great majority of the sun's emission 52.8% and 30.9%, respectively. Among invisible radiation, UVA, UVB, and UVC represent 6.3%, 1.5%, and 0.5% of the total solar energy output received on the earth's surface, respectively [5]. On earth, the solar spectrum is truncated in the UV waveband at approximately 290 nm after the absorption of stratospheric O_3. In this region, the middle wave UVR is of particular interest because of its potential to damage organisms [6]. The biological effectiveness of UVR increases logarithmically with decreasing wavelength. UVR shorter than 290 nm is absorbed by O_2, O_3, and water vapor in the upper atmosphere and does not reach at the earth's surface.

1.1.2 Nature of Ultraviolet Radiation

On the basis of biological effects, UV spectrum is further subdivided into three regions. This division of UVR was first performed in the meeting of the Second

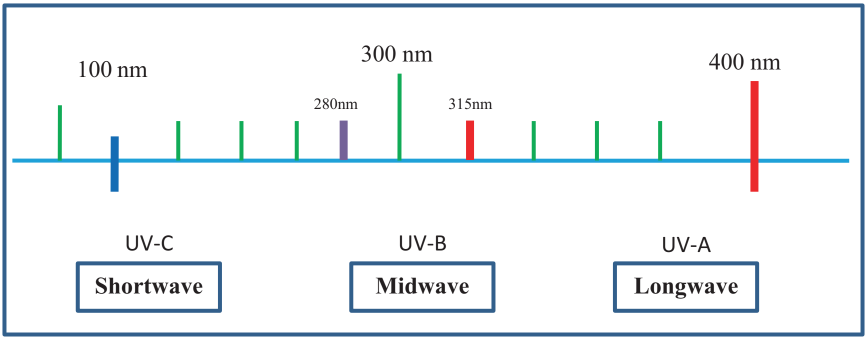

Fig. 1.1 UV regions of solar spectrum

International Congress on Light held during August 1932 at Copenhagen (Fig. 1.1). It was proposed those three spectral regions as follows:

UVA 400–315 nm
UVB 315–280 nm
UVC 280–100 nm

1.1.3 UV Regions of Solar Spectrum

However few photodermatologists and environmentalists normally define the wavelength regions of UVR as follows:

UVA 400–320 nm
UVB 320–290 nm
UVC 290–200 nm

1.1.4 Nomenclature and Units

The International Commission on Illumination (CIE) is an organization of 40 countries. It is devoted to international cooperation and exchange of information among on all matters relating to light, illumination, color, and color spaces. CIE was established in 1913 as a successor to the Commission Internationale de Photométrie. It is based in Vienna, Austria.

Radiometric units are used to characterize the sources of UVR. The terms dose (J/m^2) and dose rate (W/m^2) pertain to the energy and power, respectively [6]. The radiant energy delivered to a given area in a given time is also referred to as "fluence," "exposure dose," and "dose."

Radiometric calculation: The most frequently radiometric calculation is to determine the time for which a subject who has been prescribed a certain dose (J/cm^2)

should be exposed when the radiometer indicates an irradiance in watt/m^2. The relation between three quantities (time, dose, and irradiance) is simplified:

$$\text{Exposure time}\left(\text{min}\right) = \frac{\text{Prescribed dose}\left(\text{J/m}^2\right)}{60 \times \text{measured irradiance}\left(\text{w/m}^2\right)}$$

1.1.5 Minimum Erythemal Dose

The minimum erythemal dose (MED, J/m^2) is defined as the defined as the threshold dose that produces a noticeable erythema on a previously unexposed skin of an individual. This is determined by reddening of the skin and depends on many variables including skin pigmentation thickness of skin and exposure site.

1.1.6 Standard Erythemal Dose

The standard erythemal dose (SED, J/m^2) is equivalent to an erythemal radiant exposure of 100 J/m^2. The SED is independent of skin type, and a particular exposure dose in SED may cause erythema in fair skin but none in darker skin. The global solar UV index was developed to promote public awareness of the risks of UVR exposure.

1.1.7 UV Index

The UV index is used to aware the general public about UVR intensity. It was developed by joint effort of World Health Organization, the United Nations Environment Program, and International Commission on Non-Ionizing Radiation Protection. Further, it was established by ISO/CIE. The UVI is an international standard index which depicts the level of solar UV radiation at the earth's surface. It ranges from 0 to 11+, and the values are divided into various exposure categories. Higher index values represent greater potential for harmful effects to the human skin and eyes (Fig. 1.2).

1.1.8 Sources and Exposure of Solar UVR

Optical radiation from the sun is modified substantially, and two-thirds of the energy penetrates to ground level. Solar UVR from its path through the earth's surface is absorbed and scattered by various constituents of the atmosphere. Air molecules, particularly oxygen and nitrogen, by aerosol and dust particles and atmospheric pollutants absorb and scattered the UVR. Total solar irradiance varies with altitude. Clouds attenuate infrared radiation more than UVR.

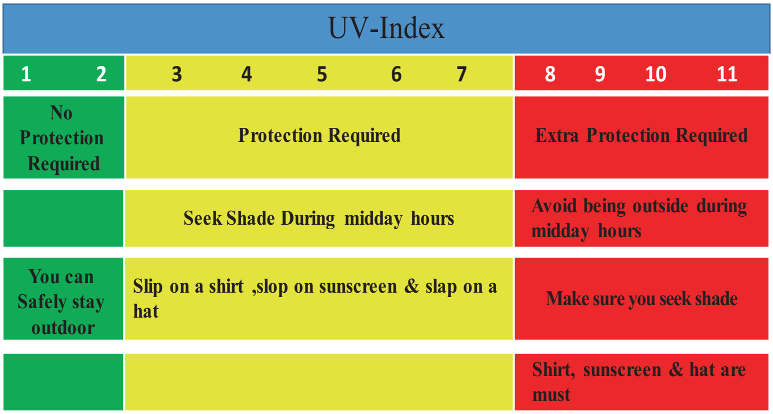

Fig. 1.2 UV index chart

Table 1.1 Thickness of O_3 layer in stratosphere at normal temperature and pressure

Position	Thickness (Dobson)	Thickness (mm)
At poles	310–430	3.10–4.30
At equatorial line	240–260	2.40–2.60
Near equatorial line	150–200	1.50–2.00
At sea level	10–50	0.10–0.50

Stratospheric ozone layer acts like umbrella to control the intensity of UVR on earth surface. Interestingly, stratosphere O_3 layer varies reasonably in thickness between 2.4 and 2.6 mm at equator and 3.1 and 4.3 mm at poles (Table 1.1). At the sea level, it is present only in traces (0.02 ppb). This has been progressively depleted as a result of accumulation of ozone-destroying chemicals in the earth's atmosphere, mostly chlorofluorocarbons (CFCs) and hydrochlorofluorocarbons (HCFCs). These chemicals are mainly used in refrigeration and air conditioning. The Nobel Prize in Chemistry was awarded in 1995 to the scientists for sounding the alarm about depletion of the earth's protective O_3 layer. It was won jointly by Mario J. Molina (MIT, USA), F.S. Rowland (University of California, USA), and Paul Curtzen (Max-Planck Institute, Germany).

1.2 Ozone Depletion

CFCs have been released into the atmosphere in sufficient quantities to damage the O_3 layer. The compounds carry chlorine to the stratosphere that acts as a catalyst to decompose O_3 by photolysis. O_3 depletion promotes to an increase in UVB on earth surface [5]. The half-life of the CFCs is between 50 and 400 years in stratosphere.