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Environmental Contaminations and Occupational Exposures Involved in Preparation of Chemotherapeutic Drugs

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1. Indroduction

Many healthcare workers are concerned about the risk of occupational exposures to hazardous drugs. Since Falck [Falck et al.,1979] reported that mutagens were detected in the urine samples of nurses involved in chemotherapy, many reports have been published about the presence of urinary mutagen [Roth et al.,1994; Burgaz et al.,1999; Kasuba et al.,1999; Lanza et al.,1999; Jakab et al.,2001; Kopjar & Garaj-Vrhovac,2001], and about the detection of unchanged hazardous drugs in the urine samples of healthcare workers [Hirst et al.,1984; Sessink et al.,1992, 1994, 1995; Ensslin et al.,1994; Minoia et al.,1998; Burgaz et al.,1999; Pethran et al.,2003]. Tomioka [Tomioka & Kumagai,2005] monitored occupational exposures to hazardous drugs by routes of exposures and the levels at which the drugs exert their effects; i.e. (i) external exposures, exposure to airborne drugs and drugs deposited on the working table; (ii) internal exposures, presence of drugs or their metabolites in blood and urine; (iii) cellular level effects, presence of mutagens in urine and frequency of sister chromatid exchanges; and (iv) effects on individual level, susceptibility to cancer and effects on reproduction. Recent improvements of analytical instruments have permitted direct monitoring of external exposures and internal exposures.

Hospital pharmacists in Japan have been required to prepare chemotherapeutic drugs. The Japanese Society of Hospital Pharmacists (JSHP) revised the "Guideline for the Handling of Antineoplastic Drugs in Hospitals" in 2005, and recommended standard precautionary measures for using the laminar flow cabinet, masks, gloves, caps, disposable nonwoven clothes, and luer-lok syringes. This guideline was based on the "NIOSH alert" by the National Institute for Occupational Safety and Health [NIOSH,2004]. In addition, the JSHP investigated occupational exposures to cyclophosphamide in several hospitals, and reported that internal exposures and external exposures varied greatly in individuals, in hospitals and even in countries. This investigation led to increased concerns among hospital pharmacists about the exposures to chemotherapeutic drugs.

Before the JSHP investigation, we have investigated whether the precautionary measures we took were adequate to prevent occupational exposures [Ikeda et al.,2007; Maeda et al.,2010]. We focused on occupational exposures to epirubicin, cyclophosphamide and ifosfamide,

and reported that the surfaces of biological safety cabinets (BSCs) and ambient environments were contaminated by these drugs during preparation by pharmacists (external exposures). However, detection frequencies and amounts of these drugs were low levels, compared with previous reports in Japan [Nabeshima et al.,2008; Yoshida et al.,2009]. In addition, no drugs were detected in sera and urine samples of healthcare workers involved in chemotherapy (internal exposures). Thus, we concluded that adequate precautionary measures and improved awareness regarding handling of chemotherapeutic drugs could reduce the risk of occupational exposures. These investigations were focused on specific drugs, however, a progress of chemotherapy increases amounts of and varieties of chemotherapeutic drug uses. Thus, more versatile methods are desired.

Multicomponent analyses are useful for monitoring environmental contaminations, such as pesticide chemicals [Lissalde et al.,2011; Miao et al.,2011] and air pollution [Skoczynska et al.,2008; Sebok et al.,2009]. However, there are only several reports in the fields of occupational exposures to healthcare workers [Larson et al.,2003; Sabatini et al.,2005; Sottani et al.,2007, 2008; Nussbaumer et al.,2010].

In this paper, we used liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) and developed multicomponent analysis procedures for chemotherapeutic drugs, and assessed the levels of environmental contaminations involved in preparation of chemotherapeutic drugs. We selected ten kinds of drugs mainly used in chemotherapy; cyclophosphamide, ifosfamide, epirubicin, doxorubicin, vindesine, vincristine, vinblastine, irinotecan, docetaxel and paclitaxel. Classification of drugs, chemical natures, regulations, uses of drugs, side effects, carcinogenicities, cytotoxicities [Goolsby & Lombardo,2006] and pregnancy categories of each drug were summarized in Table 1.

No.	Name of drugs	Regulations	Classification of drugs (chemical natures)	Main uses of drugs
1	Vindesine	Powerful drug	Vincalkaloid (antimicrotuble drug)	Leulemia, Lung cancer
2	Vincristine	Powerful drug	Vincalkaloid (antimicrotuble drug)	Leukemia, Malignant lymphoma, Multiple myeloma
3	Vinblastine	Powerful drug	Vincalkaloid (antimicrotuble drug)	Malignant lymphoma, Urothelial carcinome
4	Doxorubicin	Powerful drug	Anthracycline (anticancerous antibiotic)	Malignant lymphoma, Breast cancer, Lung cancer
5	Epirubicin	Powerful drug	Anthracycline (anticancerous antibiotic)	Leukemia, Malignant lymphoma, Breast cancer
6	Ifosfamide	Powerful drug	Mustard (alkylating drug)	Lung cancer, Prostatic cancer
7	Cyclophosphamide	Powerful drug	Mustard (alkylating drug)	Leukemia, Breast cancer, Rheumatism
8	Irinotecan	Powerful drug	Topoisomerase I inhibitor	Lung cancer, Ovarian cancer, Colorectal cancer
9	Docetaxel	Toxicant	Taxane (antimicrotuble drug)	Breast cancer, Lung cancer, Uterine cancer
10	Paclitaxel	Toxicant	Taxane (antimicrotuble drug)	Breast cancer, Lung cancer, Uterine cancer

No.	Name of drugs	Main side effects	Hazard potential		
			Carcinogenicity	Cytotoxicity	Pregnancy
1	Vindesine	Myelosuppression		Vesicant	
2	Vincristine	Peripheral neuropathy, Cardiotoxicity		Vesicant	Category D
3	Vinblastine	Myelosuppression		Vesicant	Category D
4	Doxorubicin	Delayed myelosuppression and cardiotoxicity	Probably carcinogenic	Vesicant	Category D
5	Epirubicin	Delayed myelosuppression and cardiotoxicity		Vesicant	Category D
6	Ifosfamide	Hemorrhagic cystitis		Irritant	Category D
7	Cyclophosphamide	Myelosuppression, Hemorrhagic cystitis	Carcinogenic	Irritant	Category D
8	Irinotecan	Delayed diarrhea, Myelosuppression		Non-vesicant	Category D
9	Docetaxel	Myelosuppression, Pulmonary fibrosis		Vesicant	Category D
10	Paclitaxel	Myelosuppression, Perepheral neuropathy		Vesicant	Category D

Regulations, use of drugs and side effects were authorized by the Ministry of Health, Labour and Welfare in Japan.
Carcinogenicities were classified by IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans.
Pregnancy categories were classified by U.S. Department of Health and Human Services Food and Drug Administration. Category D was "there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pfegnant women despite potential risks."

Table 1. Charactaristics of selected chemotherapeutic drugs.

2. Materials and methods

2.1 Chemicals and materials

Doxorubicin, ifosfamide, cyclophophamide and paclitaxel were purchased from Wako Pure Chemical (Osaka, Japan). 3,4-Anhydro vincristine [internal standard (IS) 1] was purchased from Toronto Research Chemicals (Toronto, Canada). Camptothecin (IS 2) was purchased from Tokyo Chemical Industry (Tokyo, Japan). Docetaxel, carminomycin (IS 3) and trofosfamide (IS 4) were purchased from Santa Cruz Biotechnology (California, USA). Irinotecan and cephalomannine (IS 5) were purchased from Sigma-Aldrich (Missouri, USA). Vincristine, vinblastine and epirubicin were kindly provided by Nippon Kayaku. Vindesine was kindly provided by Shionogi. Acetonitrile and methanol (LC-MS chromasolv) were also purchased from Sigma-Aldrich (Missouri, USA), and formic acid was purchased from Wako Pure Chemicals.

2.2 Preparation of stock solutions, working solutions and calibration standards

Vindesine was prepared in a solution of 0.1% formic acid-water to obtain a final concentration of 2 mg/ml. Camptothecin was prepared in a solution of 0.1% formic acid-methanol to obtain a final concentration of 100 μg/ml. Other drugs were prepared in a

solution of 0.1% formic acid-methanol to obtain a final concentration of 2 mg/ml. Aliquots of these solutions were stored at -80°C, then diluted in 0.1% formic acid-methanol to obtain a final concentration of 100 μg/ml each stock solution and stored at -30°C.

Stock solutions of three vincalkaloids were mixed to working solutions, containing 33.3 μg/ml of vindesine, vincristine and vinblastine, respectively. Stock solutions of other seven drugs were also mixed and diluted in 0.1% formic acid-methanol to working solutions, containing 5 μg/ml of doxorubicin, epirubicin, ifosfamide, cyclophosphamide, irinotecan, docetaxel and paclitaxel, respectively. The working solutions of internal standard mixtures were prepared by containing 100 μg/ml of 3,4-anhydro vincrisitine, and containing 10 μg/ml of carminomycin, trofosfamide, camptothecin and cephalomannine, respectively. These working solutions were also stored at -30°C. We used black Eppendorf tubes for stock solutions of anthracycline drugs and vincalkaloid drugs, and for all working solutions. The calibration standards were prepared by diluting these working solutions.

2.3 Chromatographic conditions

An Alliance 2695 HPLC separation module (Waters; Massachusetts, USA) with PDA detector, cooled autosampler and column oven was used to perform this monitoring. Chromatographic separation was achieved on an octadecyl silyl column (Inertsil® ODS-3; 50 mm×2.1 mm; particle size, 3 μm; GL Sciences, Tokyo, Japan) with a guard column (cartridge guard-column E®; 20 mm×2.0 mm; particle size, 3 μm, GL Sciences, Tokyo, Japan). Column oven was maintained at 30°C and autosampler was maintained at 5°C. The mobile phases consisted of 0.1% formic acid-water (mobile phase A) and acetonitrile (mobile phase B). A flow rate was 0.3 ml/min and gradient elution was performed in the following manner: 15% of mobile phase B to 45% over 10 min; 45% of mobile phase B to 80% over 7 min. Subsequently, the concentration of mobile phase B was linearly decreased to 15% for 1 min and equilibrated for 4 min. Total run time was 22 min.

2.4 Mass spectrometry conditions

A tandem quadrupole MS TQD (Waters; Massachusetts, USA), operated in multiple reaction monitoring (MRM) in positive electrospray ionization (ESI) mode, was used for detection and MassLynx 4.1 software was used for data acquisition and processing. MS/MS parameters (precursor ion, product ion, cone energy, collision energy and retention time) of each drug were individually optimized by QuanOptimize software and syringe pump infusion in primary mobile phase by constant flow (Table 2).

2.5 Precautionary measures and personals involved in preparation of chemotherapeutic drugs

Precautionary measures were based on “NIOSH alert” [NIOSH,2004] and “Guidelines for the Handling of Antineoplastic Drugs in Hospitals” by JSHP (Table 3). A preparation area for outpatient chemotherapy was selected as an environmental monitoring. The numbers of person involved in preparation for outpatients were eight; six men and two women, and ages were from twenty-four to forty-one. We rotated schedules regularly, and limited successive preparation time to 1 hour.

Parameters / Compounds	Precersor ion	Product ion	Cone energy (V)	Collision energy (V)	Retention time (min)
Vindesine	754.5	124.2	55	50	1.65
Vincristine	825.4	765.6	70	40	5.02
Vinblastine	811.4	224.1	60	45	5.75
3,4-Anhydro vincristine (IS 1)	807.4	747.5	65	30	6.22
Doxorubicin	544.5	397.2	20	12	6.18
Epirubicin	544.5	397.2	20	12	6.60
Carminomycin (IS 2)	514.2	307.2	20	25	8.29
Ifosfamide	261.0	153.9	45	25	7.21
Cyclophosphamide	261.0	140.3	45	30	7.63
Trofosfamide (IS 3)	323.1	153.9	30	25	12.69
Irinotecan	587.7	167.3	60	45	5.77
Camptothecin (IS 4)	349.1	305.2	50	25	9.51
Docetaxel	808.8	226.1	20	14	15.95
Paclitaxel	854.8	286.3	25	24	16.48
Cephalomannine (IS 5)	832.8	264.2	25	20	16.09

Table 2. Parameters of MS/MS analysis.

No	Precautionary measures
1	Prepare chemotherapeutic drugs in a centralized area restricted to authorized personnel with expertise in the preparatory techniques and the characteristics of these drugs.
2	Prepare these drugs in a biological safety cabinet Class II Type B.
3	Place a superabsorbent sheet on the surfaces of the preparation cabinets.
4	Use syringes with Luer-Lok-type fittings for preparing these drugs.
5	Use gowns made of a lint-free, low-permeability fabric.The gown should have a closed front, long sleeves, and elastic or knit-closed cuffs.
6	Use disposable nitrile rubbers gloves doubly, and change gloves every hour or on accidental exposures.
7	Wear disposable mask and cap.
8	Remove protective clothing carefully to avoid spreading contaminations.
9	Maintain a negative pressure in the drug vials.
10	Always close the cover of trash boxes used to dispose of these drugs.

These measures are based on the NIOSH alert, and we take measure No. 3 for additional precaution.

Table 3. Precautionary measures we took.

2.6 Sampling procedures of ambient environment

We collected wiping samples from the surfaces of the BSCs and from the surfaces of the tables inside a separated area and outside one (Fig. 1). Investigations were carried out as

soon as daily preparation for outpatients had finished and before daily cleaning-up procedures, and obtained samples were immediately extracted and measured by LC-MS/MS equipments. We took this monitoring on seven days for successive two weeks.

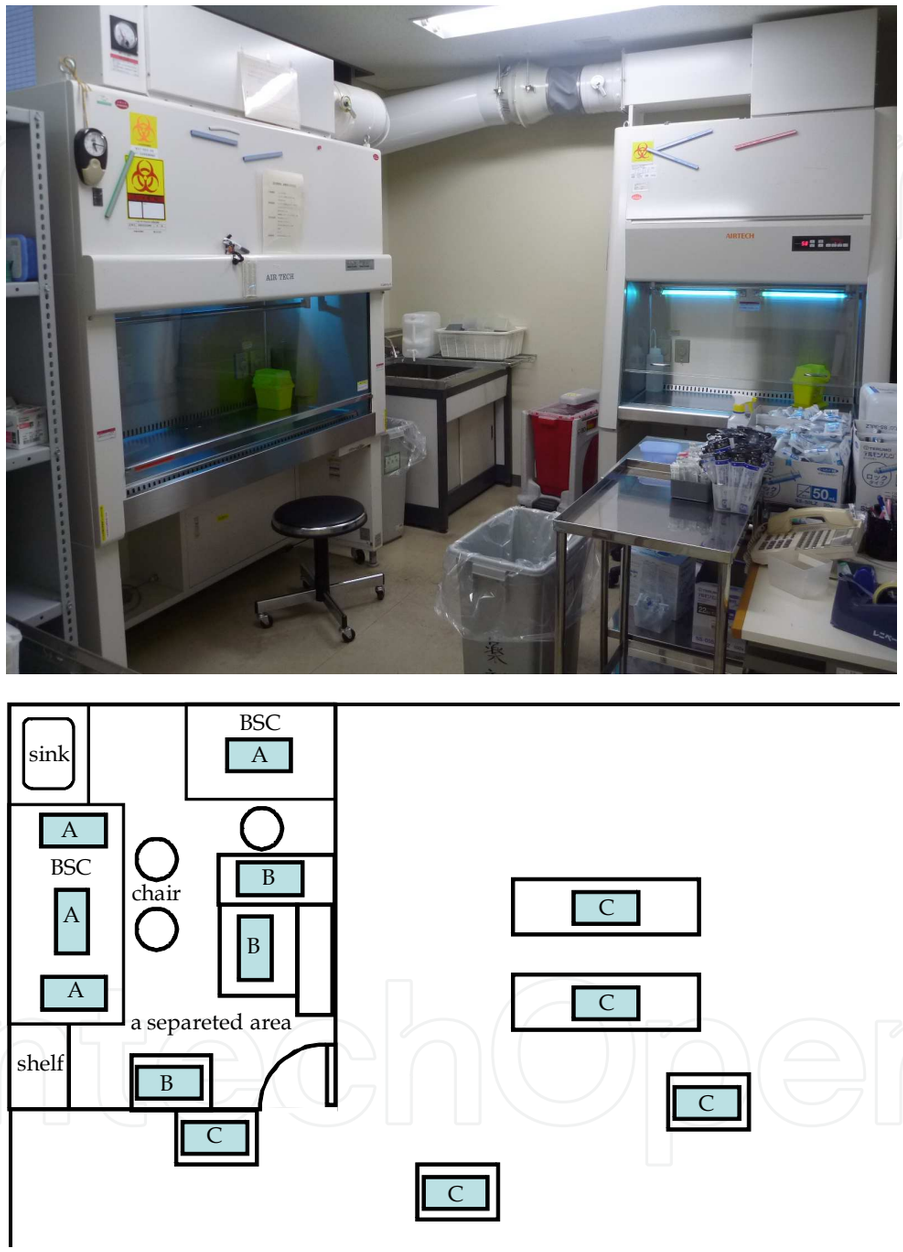

Fig. 1. Photograph of a preparation area (inside a separated area) for outpatients chemotherapy, and floor layout of a preparation area and sampling spots. A) Surfaces of the BSCs, B) Surfaces of the tables inside a separated area, C) Surfaces of the tables outside a separated area.

An extraction of wiping samples for environmental assessments was modified by our previous report [Maeda et al.,2010]. Briefly, we first applied internal standards mixtures,

containing 10 μg of 3,4-anhydro vincrisitine, 500 ng of carminomycin, trofosfamide, camptothecin and cephalomannine to sampling spots. After these spots were air-dried, we wiped 800 cm^2 area (20 cm×40cm) with a sheet of Kimwipe® S-200 (120 mm×215mm, Nippon Paper Crecia, Tokyo, Japan) wetted with 1 ml of 0.1% formic acid-70% methanol. We repeated wiping operation twice, then placed both sheets in light-blocking polypropylene conical tubes and added 8 ml of 0.1% formic acid-70% methanol. We shook these tubes for 30 min, 2,000 rotations per min. Obtained extracts were directly injected into LC-MS/MS equipments without dilution.

3. Results

All drugs were clearly detected and quantified over a total run time of 22 min. The calibration curves were fitted by the linear regression 5-1000 ng/wipe for doxorubicin, epirubicin, ifosfamide, cyclophosphamide, irinotecan and paclitaxel, 10-1000 ng/wipe for docetaxel, and 100-10000 ng/wipe for vindesine, vincristine and vinblastine, respectively.

Table 4 showed the positive ratio of detection and amounts of detected drugs. The surfaces of the BSCs were occasionally contaminated, meanwhile, contaminations in the surfaces of the tables inside a separated area and outside one were at low levels.

Sampling spots	A) Surfaces of the BSCs		B) Surfaces of the tables inside a separated area		C) Surfaces of the tables outside a separated area	
Compounds	Positive samples (n = 28)	Amounts (ng/wipe)	Positive samples (n = 14)	Amounts (ng/wipe)	Positive samples (n = 14)	Amounts (ng/wipe)
Vindesine	0	—	0	—	0	—
Vincristine	0	—	0	—	0	—
Vinblastine	0	—	0	—	0	—
Doxorubicin	5	7 ~ 114	0	—	0	—
Epirubicin	0	—	0	—	0	—
Ifosfamide	0	—	1	7	0	—
Cyclophosphamide	9	5 ~ 68	1	21	1	7
Irinotecan	0	—	0	—	0	—
Docetaxel	3	9 ~ 348	0	—	0	—
Paclitaxel	1	19	1	14	0	—

Table 4. Frequencies and amounts of drugs detected in wipe samples.

4. Discussion

Since Falck's report [Falck et al.,1979], many healthcare workers are concerned about the risk of occupational exposures to hazardous drugs. Previously, in studies of external

exposures [Sessink et al.,1992; Minoia et al.,1998; Sabatini et al.,2005; Hedmer et al.,2008] and studies in internal exposures [Hirst et al.,1984; Sessink et al.,1992, 1994, 1995; Ensslin et al.,1994; Burgaz et al.,1999; Pethran et al.,2003], cyclophosphamide was frequently used as a marker of occupational exposures because of its slight volatility and human genotoxicity [Connor et al.,2000], reproductive toxicity [Anderson et al.,1995], carcinogenicity [IARC,1981], and ease of detection [Turci et al.,2002; Barbieri et al.,2006].

We also focused on occupational exposures to several chemotherapeutic drugs including cyclophosphamide, and concluded the precautionary measures we took were adequate to prevent occupational exposures [Ikeda et al.,2007; Maeda et al.,2010].

In this paper, because a progress of chemotherapy requires more versatile monitoring, we developed a multicomponent analysis method of chemotherapeutic drugs, and assessed the levels of environmental contaminations involved in preparation of chemotherapeutic drugs. Anthracycline drugs were light sensitive and were absorbed on glass containers [Lachatre et al.,2000] and vincalkaloid drugs were absorbed on some materials of tubes [Van Tellingen et al.,1991], we selected black Eppendorf tubes for stock solutions and working solutions, and light-blocking polypropylene tubes through extraction.

We prepare chemotherapeutic drugs in three different ways; (i) prepare drugs for outpatients on the BSCs equipped on a separated area, maintained constant a negative pressure, in hospital pharmacy; (ii) prepare drugs for inpatients on the BSCs equipped on a separated area in hospital pharmacy; (iii) prepare drugs for inpatients required special care (such as pretreatment for hematopoietic stem cell transplantation) on the BSCs equipped at the corner of the nurse station in a biological clean ward. We focused on environment of preparation for outpatients, because numbers of drugs were prescribed for outpatients and fast preparations were needed.

Our multicomponent analysis method had sufficient sensitivities and had conveniences enough for regular monitoring. Lower limits of quantitation were 5 ng/wipe for doxorubicin, epirubicin, ifosfamide, cyclophosphamide, irinotecan and paclitaxel, 10 ng/wipe for docetaxel, and 100 ng/wipe for vindesine, vincristine and vinblastine, respectively.

In the environmental assessments, vindesine, vincrisitine, vinblastine, epirubicin and irinotecan were not detected. Although doxorubicin, cyclophosphamide, docetaxel and paclitaxel were occasionally detected in the surfaces of the BSCs, frequencies and amounts of drugs detected were low levels in the surfaces of the working tables inside a separated area and outside one.

Inhalation and dermal penetration were presumed to be the main routes of occupational exposures. Several researchers [McDevitt et al.,1993; Sessink et al.,1994; Minoia et al.,1998] compared the urinary cyclophosphamide excretion levels and concentrations of cyclophosphamide in air during preparation of drugs. They concluded that the amounts of cyclophosphamide inhaled were much lower than amounts of cyclophsphamide excreted in urine, and that inhalation was not the main route of exposures resulting in high levels of cyclophosphamide. Fransman [Fransman et al.,2004, 2005] reported that dermal exposure predominantly occurred on the hands and sporadically on the forehead and forearms, and he mentioned that greater than 90% exposures were prevented by using latex gloves at the time of preparations. These reports showed that dermal exposures occurred on the hands

were the main route of internal exposures. Thus, routine monitoring of unexpected environmental contaminations is very useful for preventing occupational exposures.

5. Conclusion

We developed a multicomponent analysis method of ten major chemotherapeutic drugs, and assessed the levels of environmental contaminations involved in preparation of chemotherapeutic drugs. We revealed that environmental contaminations outside BSCs were at low levels, and concluded that adequate precautionary measures and improved awareness regarding handling of chemotherapeutic drugs could reduce the risk of occupational exposures.

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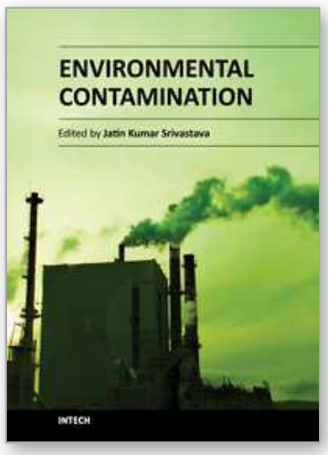

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Nature minimizes the hazards, while man maximizes them. This is not an assumption, but a basic idea of the findings of scientists from all over the world. The last two centuries have witnessed the indiscriminate development and overexploitation of natural resources by man causing alterations and impairment of our own environment. Environmental contamination is the result of the irrational use of resources at the wrong place and at the wrong time. Environmental contamination has changed the lifestyle of people virtually all over the world, and has reduced the extent of life on earth. Today, we are bound to compromises with such environmental conditions, which was not anticipated for the sustenance of humanity and other life forms. Let us find out the problem and its management within this book.

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