AN INTEGRATED APPROACH FOR ASSESSING HUMAN HEALTH RISK IN PROCESS FACILITY

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by

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Abstract

Chemical process industries are often prone to undesired incidences and accidents. Release of toxic chemicals is one of such incidences which may lead to human health hazard resulting in potential loss in process facility. In order to prevent these unwanted health effects process safety management programmes (PSM) are adopted. Process safety management involves a systematic evaluation of hazards and necessary measures to mitigate them. Continuous monitoring and effective approaches for risk modeling may prevent these catastrophic situations. The present study is conducted by developing the methodology to assess the human health risk in process facility using quantitative methods, available data and standards.

Quantitative Risk Assessment (QRA) is a process of identifying and evaluating the risk. The application of QRA in process facility involves development of methods and techniques to assess and minimize the risk as well as to help analyzing the undesired incidences together with the related consequences. Two types of approaches of QRA are presently being used for human health risk assessment. One is deterministic approach and the other is probabilistic approach. Probabilistic approach provides better estimates in certain cases where uncertainties are involved.

Probabilistic Risk Assessment (PRA) is a reliable method to quantify human health risk. This involves characterization of human health risk considering the uncertainty and variability of exposure parameters. Probabilistic analysis allows to gather information about the range and likelihood of exposure and helps decision makers to take further decision. In addition to that, Bayesian probability analysis has also been used for developing a risk model to characterize the human health risk.

In this thesis an integrated approach to assess human health risk is described and applied for past and current exposure data directly extracted from secondary sources. First, the hazards were identified and represented based on chronic studies. Again, the mixed chemical exposure is analyzed using two established statistical methods and available epidemiological information. Two exposure-response models are developed applying these data. Subsequently, the toxicity of the chemicals are assessed applying BMD approach to derive the toxicity values, the toxicity score of the chemicals as well as a safe exposure level for workplace using experimental animal data. And, finally a risk model has been developed to quantify the human health risk applying the Bayesian Monte Carlo Analysis. This risk model predicts risk using past and current exposure data. The past exposure data is the mortality data of worker from the Clydach Wales nickel refinery and the current exposure considers the high risk operations (High temperature operations and feed preparation) in process facility. The risk model compares the human health risks from past and present nickel

exposure. The sensitivity report is represented using the risk models and Advanced Monte Carlo Simulation of Latin Hypercube Sampling (LHS) which describes the relative importance of exposure parameters quantifying risk.

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impossible for me to complete the journey of the years I have passed. I , therefore, dedicate this work to them.

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List of Symbols and Abbreviations

ACGIH	American Conference of Government Industrial Hygienists
ADI	Average Lifetime Daily Intake
ADI	Acceptable Daily Intake
AIC	Akaike Information Criteria
ASTM	American Society for Testing and Material
AT	Average Time
ATSDR	Agency for Toxic Substance and Diesease Registry
BMD	Benchmark Dose
BMDL	Lower Limit of Benchmark Dose
BMR	Benchmark Response
BMDS	Benchmark Dose Software
BW	Body Weight
C	Concentration
CDF	Cumulative Distribution Function
CR	Cancer Risk
CSF	Cancer Slope Factor
DMCA	Dimensional Monte Carlo Analysis
DRM	Dose Response Modeling

DRMs	Dose Response Models
EF	Exposure Frequency
ED	Exposure Duration
EFD	Exposure Frequency and Duration
ET	Exposure Time
H_0	Null Hypothesis
H_a	Alternate Hypothesis
HHRA	Human Health Risk Assessment
HI	Hazard Index
IR	Inhalation Rate
IRIS	Integrated Risk Information System
LHS	Latin Hypercube Sampling
LOAEL	Lowest Observed Adverse Effect Level
MEE	Micro Exposure Event Analysis
MSHA	Mine Safety and Health Administration
NAS	National Academy of Science
NIOSH	National Institute for Occupational Health and Safety
NOAEL	No Observed Adverse Effect Level
OEL	Occupational Exposure Level or Limit
OSHA	Occupational Health and Safety Administration

PDF	Probability Density Function
PEA	Preliminary Exposure Assessment
PEL	Permissible Exposure Limit
POD	Point of Departure
PRA	Probabilistic Risk Assessment
QRA	Quantitative Risk Assessment
R	Risk
RBCA	Risk Based Corrective Action Framework
REL	Recommended Exposure Level
RfD	Reference Dose
s	Standard Deviation
SEHRA	Subcommittee on Environmental Health and Related Programmes
SF	Slope Factor
SMR	Standard Mortality Ratio
US.EPA	United States Environmental Protection Agency
X	Exposure Variable
x	Exposure Level
Y	Exposure Variable
Z	Exposure Variable
$\lambda(x)$	Hazard Rate

λ_0	Background Hazard Rate
β	Regression (slope) Parameter
$p(x/c)$	Prior Density Function
$p(x/y,c)$	Posterior Density Function
$p(y/x,c)$	Likelihood Function
$g(\mu/data)$	Posterior Distribution
$g(\mu)$	Prior Distribution
μ	Uniformly Distributed Input Variables
μ_d	Population Mean
μ_0	Hypothesized Mean

Chapter 1

Introduction

1.1 Introduction

Process facilities often have the possibilities of releasing toxic, flammable or process chemicals, causing fire and explosion and many other operational disruption. To control these undesired events, process safety management programmes are adopted for the protection of employee and public health as well as to restrict environmental damage. A systematic identification and evaluation of these hazards can minimize the risk and can determine the potential of catastrophe in the workplace. Process safety management is an integral part of chemical risk assessment and safety in the workplace.

Workplaces impose variety of health effects to workers from the exposure to toxic chemicals. Workers may suffer from different types of acute and chronic diseases, such as, respiratory diseases, neurological effects, reproductive and birth defects, cancer etc. from occupational exposure to toxins. Some regulatory agencies are involved in minimizing the risk from these kinds of exposure. However, still, there remains some excess risks to worker's health. Risk assessment and occupational health are

very much interrelated. Several risk assessment methods have been developed to identify and minimize the health risk at workplaces.

1.2 Background and scope of the study

This study is focused on the health risk assessment of workers involved in process facility. The cancer and non- cancer effects from chronic exposure to chemicals have been examined. The occupational health risk related to nickel exposure is studied based on some epidemiological evidences from literature within the context of past and present exposure scenarios. The case studies focusing on worker's exposure to nickel have been discussed below (NAS,1975);

The case study considered here is the Clydach nickel refinery which has been in operation since 1900. The refinery workers have reported evidence of mortality due to lung cancer and respiratory disease. The ratio of observed and expected death from lung cancer are 10.1:1, 6.2:1 and 1.3:1 during the year of 1900 -1915, 1915-1929 and 1925-1944 respectively. Some studies show that the average time interval between first joining to work and first tumor detection was 27 years and some others suggested that this interval ranged from less than 5 years to more than 40 years. In the Clydach nickel refinery, the number of observed deaths from lung cancer were 15 in process workers and 1 in non- process workers during 1929.The respiratory disease resulted in about 13 deaths in process workers and 10 in non- process workers. The number of deaths from heart disease and cerebral hemorrhage were 15 in process workers and

Table 1.1: Past exposure to nickel compounds in refineries (Source: Seilkop and Oller,2003)

Cohort	Exposure Year	Employees Number	Lung Cancer SMR	Soluble Ni (mg/m^3)	Ni sub-Sulfide (mg/m^3)	Ni Oxide (mg/m^3)
Clydach, Wales	1902-1930	1348	394	≤ 10	≤ 15	≤ 50
Ontario Sinter Plant	1926-1972	3769	261	>1	>10	>10
Kristiansand, Norway	1916-1983	4764	300	>0.5	>0.5	>2
Harjavalta, Finland	1945-1985	1388	212	0.2-0.8	0.06-0.4	-

*SMR = Standard Mortality Ratio.

17 in non- process workers. Again, the ratio of observed and expected risk was 13.8 during 1938-1947. The percentage of death from lung cancer in process workers has been higher than that of non- process workers. Some reports showed that 58% of deaths which occurred during 1938-1947 and 23% which occurred before 1944 were from lung cancer in process workers.

Another nickel refinery named Port Colborne situated in Ontario, Canada has started their production of nickel from sulfidic ore during 1918-1928. This refinery has also reported some evidence of mortality from nickel exposure. Epidemiological studies reported that the observed risk of lung cancer had been 2.2 times higher than the expected during 1930-1957. Evidences from literature showed that the workers from electrolysis has the lowest risk of death from lung cancer as the ratio of observed to expected has been 0.8:1 and the workers from furnace operation had the highest risk

Table 1.2: Present exposure to nickel compounds in refineries (Source: Seilkop and Oller,2003)

Cohort	Exposure Year	Employees Number	Lung Cancer SMR	Soluble Ni (mg/m^3)	Ni sub-Sulfide (mg/m^3)	Ni Oxide (mg/m^3)
Falconbridge, Ontario	1946-1984	11567	128	<0.3	<0.5	<0.5
INCO, Ontario	1914-1984	37117	111	<0.3	<0.5	<0.5
High Nickel Alloys,USA	1956-1988	31165	113	-	-	0.01-0.3
Clydach, Wales	1931-1984	1173	124	-	>1	>5

*SMR = Standard Mortality Ratio.

with the Standard Mortality Ratio (SMR) value 7. Some studies characterized the mortality in relation to the different types of industrial operation and age group of the workers. These studies reported that the mortality is higher in 40-49 year age group of male workers for smelting and preparation and drying processes. For the age group >50 year the roasting and reduction and other refinery processes have been highly risky areas to work. The results have also been the same for female workers except in the smelting and roasting process.

The nickel exposure in todays workplace has became lower than the past. The emphasis was given to the inhalation of nickel particles and different respiratory effects by regulatory agencies. The main focus of these studies have been to identify the association between respiratory effect and exposure to nickel particles. Currently the highly exposed workers are mainly involved in feed preparation and high temperature

operations. The exposure level is high for nickel oxide in high temperature operations and for nickel subsulfide in feed preparation. Table-1 and Table-2 show some epidemiological evidence of past and present nickel exposure in refineries. Present approaches of risk assessment have greatly reduced the hazards related to occupational chemical exposure. These approaches can be divided into two categories; the first one uses the risk assessment methods for low level of occupational exposures to estimate the risks and the other one is mainly concerned with the collection of occupational data and validation and development of risk assessment methods. The application of risk assessment techniques in regulatory agencies has been a common practice. Based on this type of study chemical safety standards are set for different ergonomics, exposure and medical surveillance programs.

The applications of risk assessment in occupational environment has been useful to identify the occupational health risks, get the attention of regulatory authorities, enforce the standards of occupational setting, minimize the risks, guide the training programs for worker safety, and finally involve some new technology to minimize the risk. However, the drawback is that the currently available risk assessment methods and techniques sometimes result in overestimates of risks and higher permissible exposure level for workplaces.

New approaches for risk assessment provide framework for identification of occupational health risks. These approaches are important for establishing components

of occupational standard setting, including, hazard communication and controlling technologies etc. The risk assessment methodologies help in reduction of risks by targeting the significant risk areas and optimizing the performance. Further,it helps to determine whether the current health standards from technical aspects and control strategies are appropriate for protecting worker health.

1.3 Objective of the research

This study is focused on the current occupational exposure level, exposure scenarios and comparative evaluation between past and present workplace exposure as well as risk assessment. The primary objective of the study is to examine whether there is any excess risk in todays nickel workplace for both cancer and non-cancer effects and evaluation based on past and present occupational health risks for standards and data. The secondary objective of this study is to do quantitative uncertainty analysis of exposure parameters.

1.4 Organization of the thesis work

The organization of this thesis includes eight chapters. The first chapter is focused on the background, scope and objective of the study. Chapter-2 discusses some selected risk assessment models, different approaches and applications in occupational health risk assessment and finally the role of regulatory agencies in setting occupational standard.

Chapter-3 discusses the methodology applied to this research and hazard identification. The exposure sources, pathways, level of exposure are discussed for nickel refinery workers in Chapter-4. Chapter-5 is focused on the toxicity of the chemicals identified from Benchmark Dose (BMDS) software and setting of recommended exposure level.

Chapter-6 includes the development of risk models based on probabilistic risk assessment (PRA) methods and comparison of finally estimated risk. In Chapter-7, sensitivity analysis for exposure parameters has been done using probabilistic analysis (Monte Carlo Simulation) and finally the last chapter discusses the conclusion of the study and further recommendations to manage risks for occupational chemical exposure.

Chapter 2

Literature Review

2.1 Introduction

Effective application of quantitative or qualitative risk assessment approaches can improve the present risk analysis and process safety management programme. The Quantitative Risk Analysis (QRA) is basically two types: deterministic and probabilistic. Deterministic approach is mainly based on some conservative estimates of inputs which provides no information about the uncertainty related to risk estimates and sources of that uncertainty. However, this approach is comparatively cheap, easy and simple and can serve when the time is limited. In contrast, the probabilistic approaches are emphasized both for variability and uncertainty related to exposure estimates. It provides further knowledge about the range and likelihood of predicted risk which helps decision makers to assess the exposure scenarios more precisely. This chapter discusses about the qualitative and quantitative approaches and risk assessment models presently available for risk assessment.

2.2 Present approaches and applications of occupational health risk assessment

The distinction between risk assessment and risk management should be well understood. Risk management is basically concerned with the reduction of risk in workplaces. On the other hand, risk assessment involves evaluation of risk. There have been two types of approaches for assessing risk: quantitative and qualitative. These approaches are discussed below;

2.2.1 Qualitative approach

Qualitative approach involves,(i) qualitative risk characterization, evaluation of potential hazards or categorizing carcinogens,(ii) ranking of chemicals and (iii) setting of safe exposure level based on some semi-quantitative approaches (Benchmark dose or no observed adverse effect level approaches). The qualitative approaches have sometimes been more useful than quantitative approaches for different regulatory agencies.

2.2.2 Quantitative approach

Quantitative Risk Assessment (QRA) basically identifies and estimates the risk of occupational diseases or injury using several useful statistical measures from exposure to toxins or many physical agents. In earlier days QRA was basically used in biostatistics or epidemiological fields. Subcommittee on Environmental Health and

Related Programs(SEHRA) first introduced application of QRA to this field of research in 1985 (Smith et al,1995). Today QRA has been an established method for assessing human health risk. The basic four steps of QRA are as follows (Smith et al,1995):(*i*) Hazard identification,(*ii*) Hazard evaluation,(*iii*) Exposure and dose response assessment and (*iv*) Risk characterization. Hazard identification involves the reviewing of undesired health effects from certain chemical exposure. The hazard evaluation discusses about the sources of exposure, magnitude of exposure, the exposed population, exposure/dose response assessment determines the association between the exposure and the response (unwanted health effect). Characterization of risk includes the estimation of risk from the chemical exposure. The QRA is more scientific and reliable than qualitative risk assessment. Data availability from epidemiology and animal or mechanistic applications are used to quantify human health risks with uncertainty factors. The result may be different from different studies depending on the assumptions and data uncertainty. However, they still fall within the same order of magnitude.

2.2.3 Regulatory agencies

The regulatory agencies involved in setting occupational standards and enforcement at federal level are mainly Occupational Safety and Health Administration (OSHA) and National Institute for Occupational Safety and Health (NIOSH). NIOSH is involved in providing, developing and recommending safety standard and OSHA is responsible for the proper assessment of risks for worker health. Another group also working in

this area is American Conference of Governmental Industrial Hygienists (ACGIH). The responsibility of ACGIH is similar as NIOSH. OSHA basically marks a qualitative risk assessment for determining the toxic potential of a chemical. Both qualitative and quantitative approaches have been adopted from time to time by these regulators for the determination of occupational health risks. NIOSH's 'Recommended Exposure Level' (REL) are mainly derived from animal and epidemiological data. This REL is similar to the PEL (Permissible Exposure Level) for OSHA and Mine Safety and Health Administration (MSHA). The qualitative and quantitative methods used by this agencies need some improved techniques and analytical methods for providing more precise result to set health standards. The present approaches are discussed below (Smith et al.,1994);

2.2.3.1 NIOSH's approach to risk assessment

Qualitative: NIOSH mainly use qualitative approach to set their REL values. The principles they follow for the assessment are: (*i*) Hazard identification focusing on risk factors and exposure for occupational diseases. (*ii*) Hazard evaluation e.g. determining the dose, the exposed population and exposure scenario. (*iii*) Determination exposure level. (*iv*) Appropriate design and analysis of health data.

Quantitative: The NIOSH's quantitative approach includes: (*i*) QRA based on animal or human data. Human data is more preferable than animal data. (*ii*) Best appropriate methods for risk assessment to assess the exposure-response data. (*iii*)

Assumptions for statistical methods and models. (*iv*) Uncertainty and sensitivity analysis for assumptions.

Acceptable risk: NIOSH has preferred the zero risk level at which no worker will suffer. Approach for defining acceptable risk is different for different regulatory agencies. The EPA has identified safe exposure level as one in million risk level. OSHA and MSHA have set some PEL which exceeded the risk level of one in thousand.

2.2.3.2 OSHA's approach to risk assessment

The principles of risk assessment methods of OSHA includes; (*i*) data evaluation, (*ii*) Exposure/dose response assessment based on animal and epidemiological studies including the low dose effects, and (*iii*) risk characterization.

2.2.4 Exposure response modeling

The appropriate utilization of epidemiological data is useful to predict human health risk. Risk models based on epidemiological data mainly require modeling of Standard Mortality Ratios (SMRs). There have been several statistical methods for modeling SMRs. These models are of two types: linear or additive risk model and multiplicative risk model. Additive risk models add the background rate of risk and multiplicative risk models multiplies the background risk. Several studies have been reported using these modeling methods. In 1992 National Institute for Occupational Safety

and Health (NIOSH) has conducted such case study for cadmium exposed population(Smith et al,1994). It was also analyzed by OSHA and EPA in separate studies. This cohort studies for cadmium exposure were mainly based on fitting the data to following risk models(Smith et al,1994);

Additive Risk Model:

$$\lambda(x) = \lambda_0 + x\beta \tag{2.1}$$

Relative Risk Model:

$$\lambda(x) = \lambda_0(1 + x\beta) \tag{2.2}$$

Here, $\lambda(x)$ is predicted hazard rate, x is exposure level, β is regression (slope) parameter and λ_0 is background hazard rate. These models were fitted to the cadmium cohort data using SAS NLIN program. This study included about 606 workers who have been employed for at least six months between 1940 and 1969 at a cadmium refinery.

2.2.5 Dose response modeling

Dose response modeling has widely been used to evaluate hazards and determine the permissible exposure limits for chemicals. In absence of epidemiological information on exposure to toxic substances risk analyst has to rely on the controlled experiments in laboratory animals to predict human health risk. Statistical models have commonly been used to derive permissible exposure limit from existing quantitative data. There are two types of dose response models for risk assessment: Mechanistic models and Tolerance distribution models. Mechanistic models assume that the probability

of developing cancer or any adverse effect is a mathematical function of the exposure dose. This type includes, one hit , multi hit and multistage model. In contrast, tolerance distribution models assume that a certain threshold level has to be exceeded for an adverse response. This includes:log-probit model,logit model,weibull model,etc. These models are generally based on several assumptions.

Zhao et al (2005) has conducted a study related to the risk assessment of chloropyrifos. Epidemiological evidences prompted to revise the toxicity values and critical effects. This study incorporated the epidemiological and experimental animal data and risk assessment of chloropyrifos using dose response modeling. The method included three steps for deriving RfD using BMD analysis. In first step the critical effects for the chemical have been identified. Secondly,the choice of appropriate species and finally the RfD was derived using appropriate uncertainty factor using supporting documents.

2.2.6 Human health risk considerations

Risk estimates using QRA in occupational exposure situation results in overestimation of predicted risk. The considerations that should be taken into account while assessing human health risk are discussed below;

Interspecies variability: The selection of animal species is an important consideration. The sensitivity of all species to a certain chemical may not be the same. It also depends on the chemical type that the animal is exposed. Human are sometimes

more sensitive than the test species and sometimes less. So, appropriate animal to human conversion factor should be used to derive the human equivalent dose. The conversion factors are based on some reliable data. In absence of data, conversion formula can be used to derive the human equivalent dose.

Intraspecies variability: Different human may react differently from the exposure to same toxic substance. So, the dose response curve for each individual differs from healthy to sensitive human. Researchers have examined this human heterogeneity of variation in response from in vivo and in vitro studies from time to time. So, the heterogeneity of human is an important consideration in risk assessment. This obviously plays a significant role in occupational health and safety to protect worker health.

Epidemiology: The results from animal studies and epidemiological data should be coincided with each other. Sometimes, the results from animal studies could lead to a wrong decision. So, it should be validated using epidemiological data.

2.3 Human health risk modeling

The aspects of risk assessment framework can be discussed under the the following headings.(i) Risk assessment framework developed by the American Society for Testing and Materials (ASTM),(ii) Preliminary Exposure Assessment (PEA) by the State of California, (iii) Risk assessment framework of US EPA and (iv) Probabilistic risk assessment. The current human health risk modeling frameworks are described below

(Ricci, 2006);

2.3.1 The ASTM/Risk-based corrective action framework

The ASTM's Risk-Based Corrective Action framework (RBCA) has adopted two basic risk models for both carcinogenic and non-carcinogenic end point;

$$R_{cancer} = ADI[mg/kg - day] * CSF[probability/mg/kg - day]^{-1} \tag{2.3}$$

$$HI_{non-carcinogens} = \frac{ADI[mg/kg - day]}{RfD[mg/kg - day]} \tag{2.4}$$

where, R is risk, ADI is average lifetime daily intake, CSF is cancer slope factor, HI is hazard index and RfD is reference dose. The cancer slope factor and reference dose can be found in IRIS database.

2.3.2 The state of California Preliminary Exposure Assessment(PEA) framework

This framework is similar to the RBCA framework for assessing risk. The methods assess the risks from various pollutant from various exposure pathways. The risk model for all pathways is given below;

$$R_{cancer} = \sum(SF * ADI) \tag{2.5}$$

$$HI_{non-carcinogens} = \sum \frac{Intake}{RfD} \tag{2.6}$$

where, SF is slope factor, ADI is average daily intake and RfD. The intake is calculated by the following equation.

$$Intake[mg/kg - day] = \frac{(C * IR * EF * ET * ED)}{(BW * AT)} \tag{2.7}$$

where, C is concentration in exposed medium $[mg/m^3]$, IR is inhalation/ingestion rate, ET is exposure time $[hours/day]$, EF is frequency of exposure $[days/year]$, ED duration of exposure $[years]$ and BW body weight $[kg]$.

2.3.3 US EPA risk assessment framework

The US EPA risk assessment framework follows the following steps; (i) data collection and evaluation, (ii) exposure assessment, (iii) toxicity assessment and (iv) risk characterization. The equation they adopted to calculate Intake is,

$$I = \frac{(C * CR * EFD)}{(BW * \frac{1}{AT})} \tag{2.8}$$

where, I is intake, C is concentration, CR is contact rate, EFD is exposure frequency and duration, BW is body weight and AT average time.

2.3.4 Probabilistic Risk Assessment (PRA)

Probabilistic risk assessment is useful for exposure assessment of maximally exposed population and important tool for decision makers to identify risk. It is also important to quantify the uncertainty and variability into the model input parameters. There are various methods of propagating uncertainty and variability,i.g. numerical methods, analytical methods etc. The present approaches for probabilistic risk assessment are (i) Dimensional Monte-carlo Analysis (DMCA), (ii) Micro Exposure Event Analysis (MEE) and (iii) Geospatial Statistics and Bayesian Analysis (US EPA, 2001). The PRA approaches explain more about the uncertainty and variability in the risk estimates. It requires sufficient data collection, resources and time. PRA provides

confidence bounds (upper and lower) for the risk estimates and finally gives more reliable estimate than traditional deterministic approaches. USEPA has preferred tiered approach for Human Health Risk Assessment (HHRA). Figure-2-1 shows an example of the tired approach;

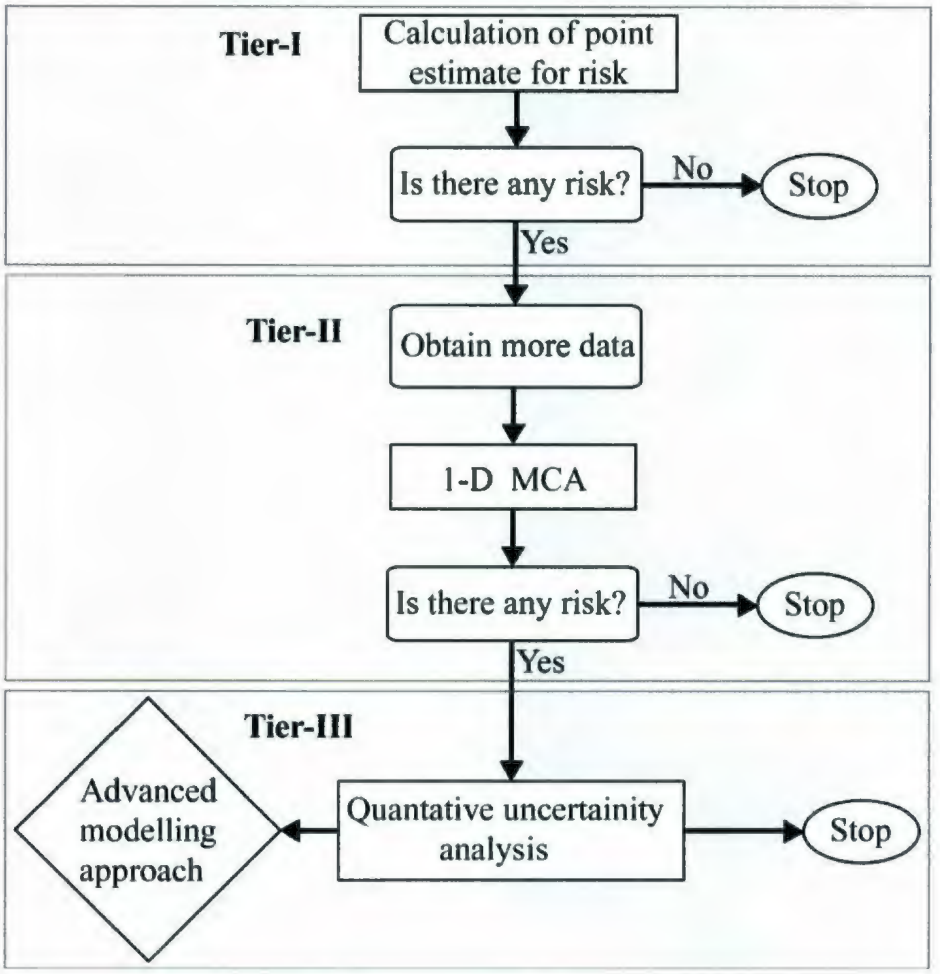

Figure 2.1: Example of tired approach for probabilistic risk assessment

Chapter 3

Human Health Risk Assessment

3.1 Introduction

Several quantitative approaches have been used for the assessment of human health risk in occupational environment. Extensive studies were carried out based on epidemiological and animal information for chemicals. However, still, there remains some uncertainties related to past exposure, mixed exposure to chemicals and insufficient effort to estimate small risks. This study is an attempt to reduce the uncertainties related to risk assessment considering past drawbacks with available data. This chapter describes the methodology adopted for this research to assess human health risk in process facility.

3.2 Methodology

The human health risk assessment is a step by step process where the risk is quantified by some established statistical methods. The basic steps involved in risk assessment process for occupational environments which have been demonstrated in this research are discussed below;

Hazard identification: Hazard identification is the first step in the risk assessment process. It includes evidence from epidemiological studies, animal studies and some up to date exposure data. This step identifies the adverse effect due to exposure to toxic substances.

Exposure assessment: Exposure assessment determines the relationship between unwanted health effect and the magnitude of exposure. This describes the magnitude and significance of exposures, potential sources of exposure, level of exposure and exposure pathways. Usually, data from epidemiological studies are used for assessing the exposure in workplaces.

Toxicity assessment: Toxicity assessment describes the biological effect of toxic dose in the target organ. Typically, the dose response models involve probability of unwanted health effect resulted from the chemical substances. This is mainly based on some animal data and principles of toxicology.

Risk characterization: Risk characterization integrates the results from hazard identification, exposure assessment and toxicity assessment. This step further evaluates the estimated risk. The evaluation of estimated risk based on acceptance criteria could help minimize the unacceptable risk to an acceptable level.

Uncertainty and sensitivity analysis: Sometimes quantitative approaches give biased estimate which can be reduced by the uncertainty analysis. Sensitivity analysis describes the significance of the exposure parameters considered into the risk estimates.

The flow chart (Figure-3.1) shows the steps adopted for this research.

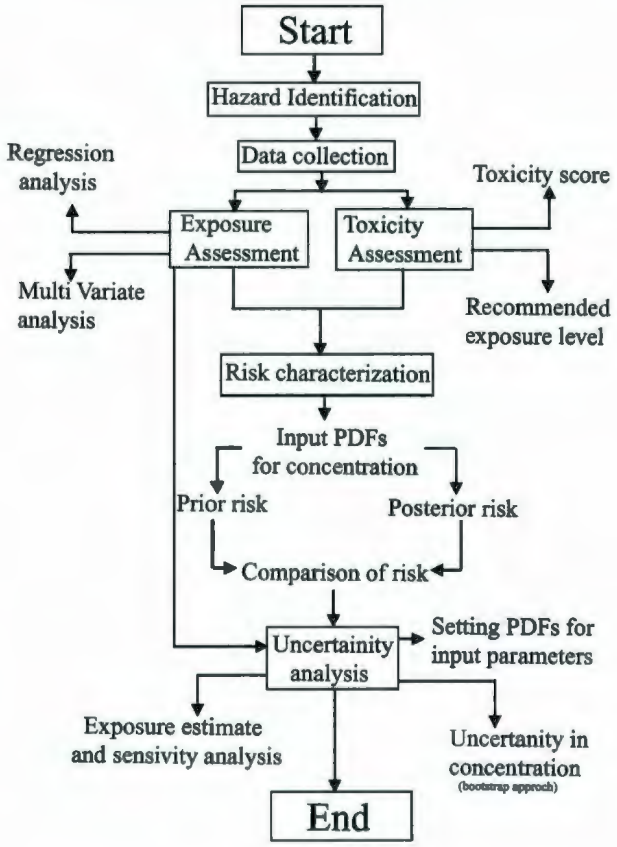

Figure 3.1: Risk assessment methodology

3.3 Chronic exposure to nickel by inhalation and health effects

The exposure to nickel compounds may cause several health effects followed by their different routes of exposure. The major routes of exposure are inhalation, oral and

dermal. The discussion mainly involves the effects of chronic exposure (365 days or more) from the inhalation of nickel compounds. Most of the evidence based on human studies are chronic occupational nickel exposure. Those studies are concerned with the toxicity of nickel compounds by estimating the relative risk, standard mortality ratios and incidences of cancer related deaths. These studies revealed an increased risk of lung and nasal cancer risk of nickel exposed workers. Table-3.1 summarizes the toxicological evidence from several human and animal studies. Table-3.1 describes different types of health effects related to the inhalation of nickel compounds.

3.4 Toxicity and carcinogenesis of nickel compounds

The discussion in this section has been compiled from several literatures and depicted below. The toxicity of nickel compound depends on its solubility to water. The soluble compounds are more toxic than the less soluble compounds whereas the less soluble compounds are more carcinogenic in nature. Again, the principal health effects are associated mainly with their major routes of exposure. 'Nickel sulfate is the most toxic compound as its solubility is higher than other nickel compounds. In contrast nickel oxide or nickel subsulfide is less toxic but they are more carcinogenic in nature' (ATSDR,2005). The lung cancer risk has not been the same for the exposure to all forms of nickel. From the dose response relationship based on some animal studies and epidemiological evidence, it has been identified that the oxidic and sulfidic nickel as complete carcinogen and soluble nickel as tumor promoter. From these experimentations, nickel subsulfide was identified as the strongest carcinogen for respiratory

cancer risks. EPA has classified nickel refinery dust and nickel subsulfide as group A carcinogens for lung and nasal cancers.

Based on several studies and assessment of nickel compounds, such as, epidemiological studies, carcinogenicity studies in experimental animals, and several types of other relevant data, it is now established that nickel compounds can generate nickel ions at critical sites in their target cells. According to IRIS data, Nickel compounds are carcinogenic to humans (Group 1). Metallic nickel is possibly carcinogenic to humans (Group 2B). Based on adequate evidence from animal and epidemiological studies, the nickel sulfate, and of the combinations of nickel sulfides and oxides encountered in the nickel refining industry are the known human carcinogens. Nickel subsulfide has been identified as the strongest carcinogen for respiratory cancer risks (ATSDR,2005). Chronic exposure to nickel subsulfide, nickel oxide and nickel sulfate has been reported in different animal studies. The results of these studies showed increases in lung tumors, e.g., Adenomas, adenocarcinomas, squamous cell carcinomas, and fibrosarcoma from the exposure to nickel subsulfide (ATSDR,2005).

3.5 Summary

This chapter describes the methodology adopted for this research and the major steps involved in it. It further discusses about the hazard identification step based on the evidence from literature. Hazard identification includes the chronic studies from literature describing the unwanted health effects from nickel exposure.

Table 3.1: Chronic exposure by inhalation to nickel and health effects (Source: ATSDR,2005)

Health effect	Exposed species	Exposure duration	LOAEL* mg/m^3	Chemical
Death	Rat	21 months;4-5d/wk;6hr/d	15	Metallic
	Rat	78 months;5d/wk;6hr/d	0.7	Subsulfide
	Rat	31 months;7d/wk;23hr/d	0.06	Oxide
	Mouse	21 months;4-5d/wk;6hr/d	15	Metallic
	Gn pig	21 months;4-5d/wk;6hr/d	15	Metallic
Renal	Human	occupational	0.75	Sulfate, chloride
Respiratory	Rat	2 months;5d/wk;6hr/d	0.5	Oxide
	Rat	2 months;5d/wk;6hr/d	0.11	Subsulfide
	Rat	2 months;5d/wk;6hr/d	0.11	Sulfate
	Rat	78 months;5d/wk;6hr/d	0.7	Subsulfide
	Rat	31 months;7d/wk;23hr/d	0.06	Oxide
	Rat	12 months;5d/wk;7hr/d	0.2	Oxide
	Mouse	2 months;5d/wk;6hr/d	1	Oxide
	Mouse	2 months;6d/wk;5hr/d	0.44	Subsulfide
	Mouse	2 months;5d/wk;6hr/d	0.11	Sulfate
Immuno	Rat	2 months;5d/wk;6hr/d	0.5	Oxide
	Rat	2 months;6d/wk;5hr/d	0.11	Subsulfide
	Rat	2 months;5d/wk;6hr/d	0.11	Sulfate
Cancer	Human	occupational	10	Sol.and less sol. forms combined
	Human	occupational	1	Soluble
	Rat	2 months;5d/wk;6hr/d	1	Oxide
	Rat	2 months;6d/wk;5hr/d	0.73	Subsulfide
	Rat	78 months;5d/wk;6hr/d	0.7	Subsulfide

*LOAEL = lowest-observed-adverse-effect level.

Chapter 4

Exposure Assessment

4.1 Introduction

Exposure response models for risk assessment are important to assess the relationship between the exposure and associated adverse effect. The exposure response models show the specific magnitude of exposure. In this study two damage function have been developed based on the available past and present exposure data. The exposure-reponse models used in this chapter can be written as,

$$R = f(X, Y, Z.....) \tag{4.1}$$

where, X,Y,Z are exposure parameters and R represents risk. The dependent and independent variables were assumed to be non-negative continuous variables. The most common and established methods for developing relationship between dependent and independent variables are; classical multiple linear regression analysis and multivariate analysis. These two methods have been used to describe the relationship between exposure and response. Steps involved in statistical model development are introduced in Figure-4.1.

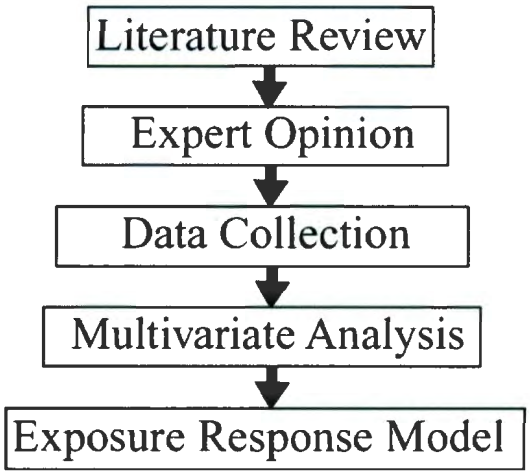

Figure 4.1: A step by step process for exposure response model development

4.2 Inhalation and absorption of nickel in human

Absorption of nickel in human lung depends on it's solubility. It has been assumed that approximately 20-35% (ATSDR,2005) of inhaled nickel is absorbed into the blood system. The remaining is expected to be swallowed and the absorbed nickel is excreted with urine. The deposition of nickel particles in upper and lower respiratory tract and absorption to blood stream depends on it's particle size. The larger the particle size the less the deposition. Large particles (5-30μm)remains in nasopharygeal area with initial impact; smaller particles (1-5μm) enter into the trachea and bronchiolar region and deposits by sedimentation;the smallest particles (1μm) deposits into alveolar region of the lungs by diffusion and electro-static precipitation (ATSDR,2005). Some studies indicate that less soluble compounds tend to remain in nasal mucosa and soluble compounds deposit into lung region. However, this process also depends on the concentration levels of nickel compounds. Again, it was suggested that the

absorbed nickel level in serum or urine is almost same for sensitive and healthy individual. Animal studies indicate that the retention rate is higher for less soluble compounds in lung. Nickel retention has been 6-10 times higher for such less soluble as nickel subsulfide than the soluble compounds (ATSDR,2005). Some earlier studies investigated the retention of nickel in human body. It has been reported that approximately 75% calculated intake is retained within the body and the remaining 25% expired depending on the particle size (NAS,1975).

4.3 Exposure to dust particles in nickel refineries

Exposure to nickel and nickel containing compounds mainly occur through airborne dust particles in refineries. The present operations involved in producing nickel are concentrating, roasting, smelting, converting and refining. These are basically called pyrometallurgical processes. These pyrometallurgical operations are high temperature operation which produces huge amount of dust particles. The Figure-4.2 (NAS,1975) shows basic steps involved in a nickel refining process. The major compounds that remain in dust particles of nickel refinery are nickel sulfate, nickel subsulfide and nickel oxide. The Table-4.1 describes compounds of typical refinery dust.

4.4 Nickel exposure to refinery workers

The past and present exposure data have been gathered to identify the past and present exposure scenarios, level of exposure and to estimate maximum exposure

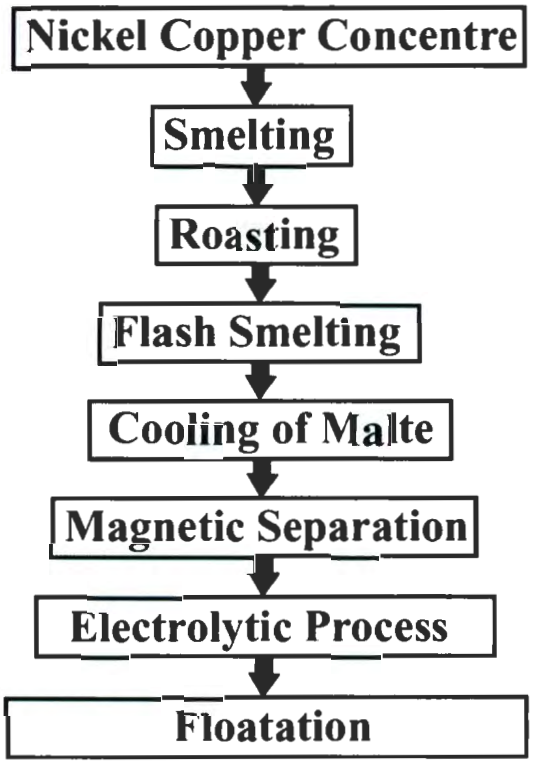

Figure 4.2: A nickel refining process

dose.

4.4.1 Exposure scenario

Epidemiological studies revealed the past exposure scenario of nickel workers. The respiratory risk tends to be associated with the specific operation from refining process. Earlier roasting and conversion of nickel sulfide to nickel oxide were identified as hazardous operations for developing cancers (NAS, 1975). Now the improved technologies have diminished the associated cancer risks.

Today the nickel exposure has been lower than the past. Several epidemiological and animal studies were carried out to examine the cancer risk associated with low level

Table 4.1: Dust particle from refineries mainly consists of following compounds (Source: NAS,1975)

Compound	Fraction (%)
Cupric oxide, CuO	3.4
Nickel sulfate, $NiSO_4.6H_2O$	20.0
Nickel subsulfide, Ni_3S_2	57.0
Nickel oxide, NiO	6.3
Cobalt oxide, CoO	1.0

nickel exposure. In Canada, the nickel workers mainly exposed through milling, feed preparation and high temperature operation. The exposure may vary from operation to operation,with nickel concentration level,with particle size distribution etc. However, the particle size in the Canadian operations is smaller like, respiratory or thoracic size. The high risk workers are mainly involved in high temperature operation and feed preparation where the oxidic nickel concentration is high in the high temperature operations and the concentration of sulfidic nickel is higher in feed preparation (Sivulka et al., 2007). In the later part of refining process oxidic nickel concentration becomes low. The concentration of metallic nickel is high at the end stage of these processes where the packing and shipping is carried out. The soluble nickel level is not much higher in Canada than compared to other countries (Sivulka et al., 2007).

4.4.2 Level of exposure

The level of exposure is described by the past and present exposure data (see Appendix-A). The present exposure has been characterized by the mean inhalable nickel refinery dust levels and nickel species from high temperature operations and

feed preparation. Past exposure data were taken from the Clydach ,Wales refinery worker's mortality data. Two exposure -response models have been developed based on these data. The unit for exposure is mg/m^3 considered for this analysis. Before developing model , the exposure data were analyzed to characterize the exposure response relationship. The following analysis of the exposure and response variables have been carried out using the software package Minitab version-15.

4.4.2.1 Exposure-response model-1

The nickel dust was taken as the dependent variable and the four forms of nickel e.g, metallic, soluble, oxidic, sulfidic considered as independent variables. The descriptive statistics for the variables are introduced in the Table-4.2.

The cluster analysis for the variables were performed to rank the variables.The clus-

Table 4.2: Descriptive statistics of nickel concentration (Source: Sivulka et al, 2007)

Variable	Mean	StDev	Minimum	Median	Maximum
Ni dust	0.448	0.291	0.208	0.371	1.000
Metallic	0.032	0.016	0.013	0.031	0.060
Soluble	0.026	0.011	0.012	0.026	0.040
Oxidic	0.271	0.226	0.055	0.192	0.680
Sulfidic	0.119	0.094	0.0230	0.099	0.240

ter analysis (Figure-4.3) shows that the sulfidic nickel exposure can be represented as separate variable as the level of similarity is less than the other variables. Figure-4.3 shows that the metallic, soluble and oxidic have the same level of similarity. Table-4.3 represents how the clusters are joined in three steps.

Paired T-test has been performed to analyze the independent variables more pre-

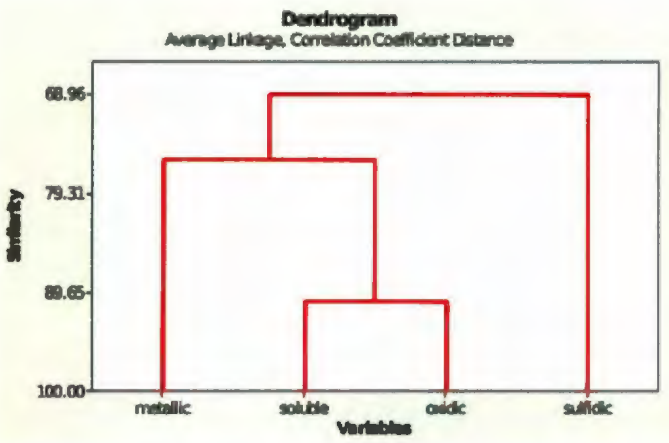

Figure 4.3: Dendrogram of exposure variables vs similarity

Table 4.3: Correlation coefficient distance, average linkage amalgamation steps

Step	Number of Clusters	Similarity Level	Distance Level	Clusters joined		New Clusters	No. of obs. in Clusters
1	3	90.5869	0.1882	2	3	2	2
2	2	75.8452	0.4830	1	2	1	3
3	1	68.9629	0.6207	1	4	1	4

cisely.

$H_0 : \mu_d = \mu_0 \quad vs \quad H_a : \mu_d \neq \mu_0$

where, μ_d is the population mean of the differences and μ_0 is the hypothesized mean of the differences. The confidence interval for the mean difference between the two

Table 4.4: Paired T for metallic - oxidic

	Mean	StDev	SE Mean
Metallic	0.0322	0.0169	0.0069
Oxidic	0.2713	0.2265	0.0925
Difference	-0.2392	0.2219	0.0906

*95%. CI for mean difference: (-0.4721, -0.0063)

*T-Test of mean difference=0 (vs $\neq 0$) : $T - Value = -2.64, P - Value = 0.046$

exposures does not include zero, which suggests a difference between them. The P-value (P=0.046) further suggests that the data are inconsistent with $H_0 : \mu_d = 0$, that is, the exposures are not equal. Specifically, oxidic nickel exposure (mean=0.2713) is higher than exposure to metallic nickel (mean=0.0322). And, thus, this test shows that oxidic exposure would be a preferable variable to use than metallic.

The results from paired T test for metallic and soluble nickel exposure is given below;

$H_0 : \mu_d = \mu_0 \quad vs \quad H_a : \mu_d \neq \mu_0$

where, μ_d is the population mean of the differences and μ_0 is the hypothesized mean of the differences. The P-value (P=0.248) shows that the data are consistent with

Table 4.5: Paired T for metallic - soluble

	Mean	StDev	SE Mean
Metallic	0.0321	0.0168	0.0068
Soluble	0.0260	0.0116	0.0047
Difference	0.0061	0.0115	0.0047

*95 perc. CI for mean difference:(-0.00597, 0.01830)

*T-Test of mean difference = 0(vs$\neq$ 0) : $T - Value = 1.31, P - Value = 0.248$

$H_0 : \mu_d d = 0$, that is, the exposures are equal.

The best subset is derived in Table-4.6 to see the best suited exposure variables for the response variable as nickel dust. The best subset is selected based on the lowest C_p value and highest $R - sq$ value (the highlighted ones in Table-4.6). The better model for the response variable would be either with the metallic, oxidic and sulfidic exposure or with the soluble, oxidic and sulfidic exposure as independent variables.

Multiple regression analysis has been used to derive a regression model for expressing

Table 4.6: Stepwise regression analysis results

Vars	R-sq	R-sq(adj)	Mallows C_p	S	Met.	Sol.	Oxi.	Sul.
1	88.6	85.8	14390.5	0.1097			X	
1	64.6	55.8	44727.1	0.1934		X		
1	40.1	25.2	75732.6	0.2517				X
1	24.0	5.0	96146.4	0.2836	X			
2	99.5	99.2	612.4	0.02613			X	X
2	93.2	88.6	8631.8	0.09813	X		X	
2	89.1	81.8	13804.0	0.1241		X	X	
2	82.9	71.5	21668.0	0.1554		X		X
3	**100.0**	**100.0**	**7.1**	**0.0029332**	**X**		**X**	**X**
3	**100.0**	**100.0**	**13.2**	**0.0043339**		**X**	**X**	**X**
3	98.7	96.7	1689.2	0.0531	X	X	X	
3	98.3	95.7	2177.1	0.0603	X	X		X

*Met.=Metalic, Sol.= Soluble, Oxi.=Oxidic and Sul.=Sulfidic

Table 4.7: Results of exposure-response model-1

Parameter	Estimate	Standard error	P value
Background	-0.0109	0.0053	0.179
Soluble	2.94	0.2842	0.009
Oxidic	0.931	0.0149	0.000
Sulfidic	1.09	0.0219	0.000

the relationship between the exposures and the response variables. The exposure-response model is,

$$Ni_{dust} = -0.0109 + 2.94 * (Soluble) + 0.931 * (Oxidic) + 1.09 * (Sulfidic) \qquad (4.2)$$

The P-value (Table-4.7) shows that the oxidic, soluble and sulfidic nickel exposure is significantly related to the response variable.

4.4.2.2 Exposure-response model-2

The relationship between SMR and nickel compounds is developed based on lung cancer mortality data which has been taken from ATSDR,2005 and the page numbers

are marked in the Appendix -A. The SMR were taken as dependent or response variable and the nickel compounds as independent or exposure variables. Before deriving the regression model, multivariate analysis has been carried out to see the significance of the independent variables.

Multivariate analysis is a statistical method to analyze the relative importance of

Table 4.8: Descriptive statistics of nickel concentration and SMR (Source: ATSDR,2005)

Variable	Mean	StDev	Minimum	Median	Maximum
SMR	5.016	2.954	1.330	5.230	11.400
Sulfidic	11.250	3.873	7.500	11.250	15.000
Oxidic	37.50	12.91	25.00	37.50	50.00
Soluble	7.500	2.582	5.000	7.500	10.000
Metallic	11.250	3.873	7.500	11.250	15.000

the variables. This has been done for the independent or exposure variables of the second exposure response model. Table-4.10 gives a summary of the decomposition of variables. The column labeled with Inertia is the x^2/n value accounted for by each component. The inertia of 1, 26.79%, 26.79%, 26.79% and 19.64% are accounted for by the first through fourth exposure variables, respectively. In Table-4.10 the column labeled Qual, or quality, is the proportion of the column inertia represented by the all calculated components. The sulfidic nickel exposure (high,low) are best represented by the two component breakdown with Qua =0.731, while the metallic exposure is the least represented with Qual = 0.001. The column labeled Mass is the proportion of the class in the whole data set and the column labeled Inert is the proportion of inertia contributed by each column. In the data set, all of the exposure variables show

Table 4.9: Analysis of indicator matrix

Axis	Inertia	Proportion	Cumulative
1	0.2679	0.2679	0.2679
2	0.2679	0.2679	0.5357
3	0.2679	0.2679	0.8036
4	0.1964	0.1964	1.0000
Total	1.0000		

Table 4.10: Column contributions

					Comp. 1			Comp. 2		
ID	Name	Qual	Mass	Inert	Coord	Corr	Contr	Coord	Corr	Contr
sul	high	0.731	0.133	0.117	-0.699	0.559	0.243	0.388	0.172	0.075
sul	low	0.731	0.117	0.133	**0.799**	**0.559**	**0.278**	-0.443	0.172	0.086
oxi	high	0.714	0.117	0.133	0.003	0.000	0.000	**0.903**	**0.714**	**0.356**
oxi	low	0.714	0.133	0.117	-0.003	0.000	0.000	-0.791	**0.714**	**0.311**
sol	high	0.696	0.133	0.117	0.669	0.511	0.223	0.403	0.185	0.081
sol	low	0.696	0.117	0.133	-0.764	0.511	**0.254**	-0.460	0.185	0.092
met	high	0.001	0.117	0.133	-0.038	0.001	0.001	0.000	0.000	0.000
met	low	0.001	0.133	0.117	0.033	0.001	0.001	-0.000	0.000	0.000

the same result for these two categories. For each of the two components (axes); The column labeled Coord gives the column coordinates. Low sulfidic nickel exposure has the largest absolute coordinates for component 1 and high oxidic exposure has the largest absolute coordinate for component 2. The column labeled Corr represents the contribution of the respective component to the inertia of the row. Here, Component 1 accounts for the highest value of low sulfidic nickel exposure and high +low oxidic nickel exposure gives the highest value for component 2. Contr, the contribution of the row to the axis inertia, shows low sulfidic and soluble nickel exposure contributing the most to Component 1 (Contr=0.278 and 0.254, respectively). Component 2, on the other hand accounts for highest value of low and high oxidic nickel exposure.

As the contribution values for Component 1 indicate, high sulfidic,oxidic and soluble nickel exposure are most distant from the origin. Low exposure to sulfidic ,oxidic and soluble nickel are near to the origin of component 1. High sulfidic and low oxidic exposures are near the origin of component 2 and High oxidic and low exposures are sulfidic distant from the origin of component 2.

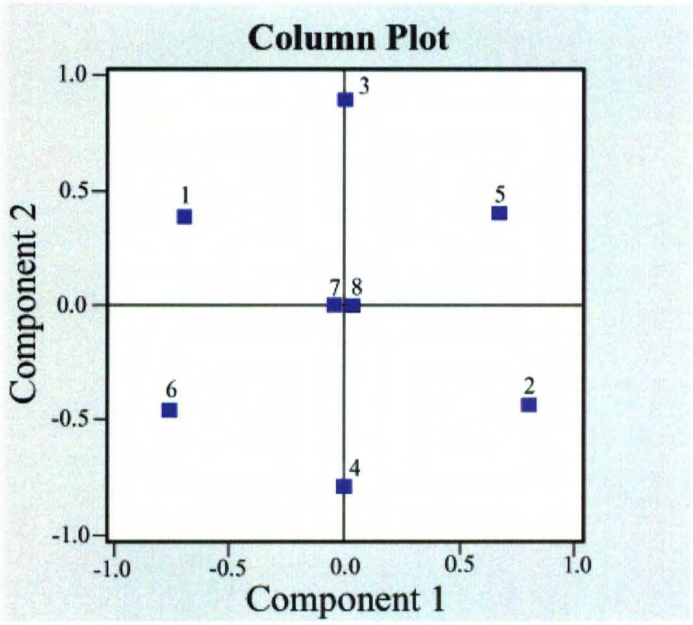

Figure 4.4: Column plot

The exposure-response model is;

$$\log(SMR) = -0.347 + 0.657 * (Sulfidic) + 0.591 * (Soluble) \tag{4.3}$$

Based on the analysis, we can conclude that the lung cancer standard mortality ratio is significantly related to sulfidic and soluble nickel exposure. Exposure to oxidic and metallic nickel is not significantly related to the response variable.

For this analysis, a 2k-factorial Design was performed where 1 represents low and

Table 4.11: Results of exposure-response model-2

Parameter	Estimate	Standard error	P value
Background	-0.347	0.5799	0.561
Sulfidic	0.657	0.2631	0.028
Soluble	0.591	0.2631	0.044

2 represents high exposure level. The interaction plot (Figure-4.5) shows that there has been an interaction between oxidic and soluble nickel at low level of exposure.The main effect plot (Figure-4.6) shows that the sulfidic and soluble nickel exposure increases the SMR with the increasing level of exposure. The SMR is high for low level oxidic nickel exposure and low for high level oxidic exposure. For metallic nickel exposure the SMR remains same for both level of exposure.

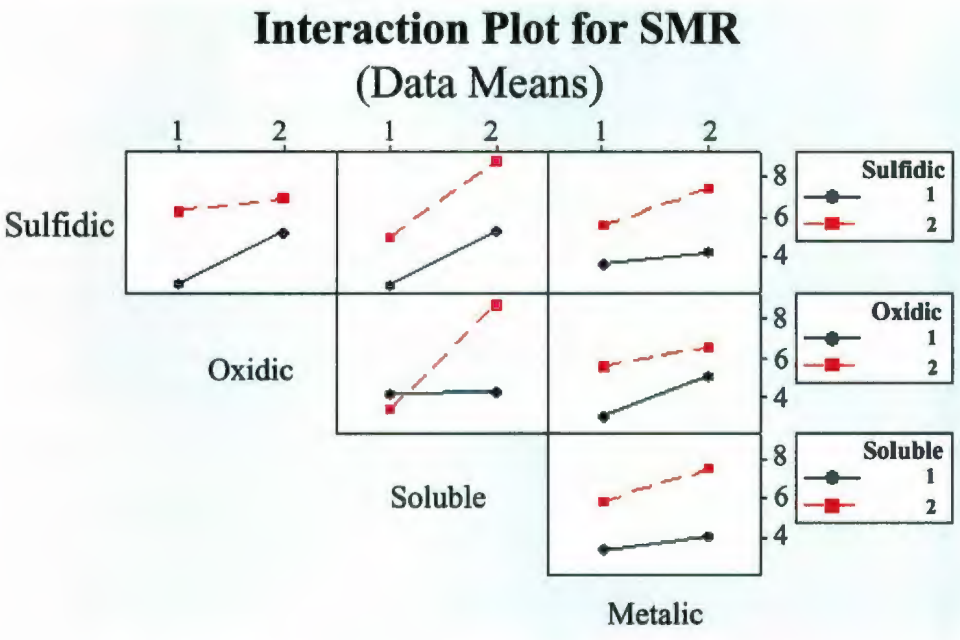

Figure 4.5: Interaction plot of exposure variables

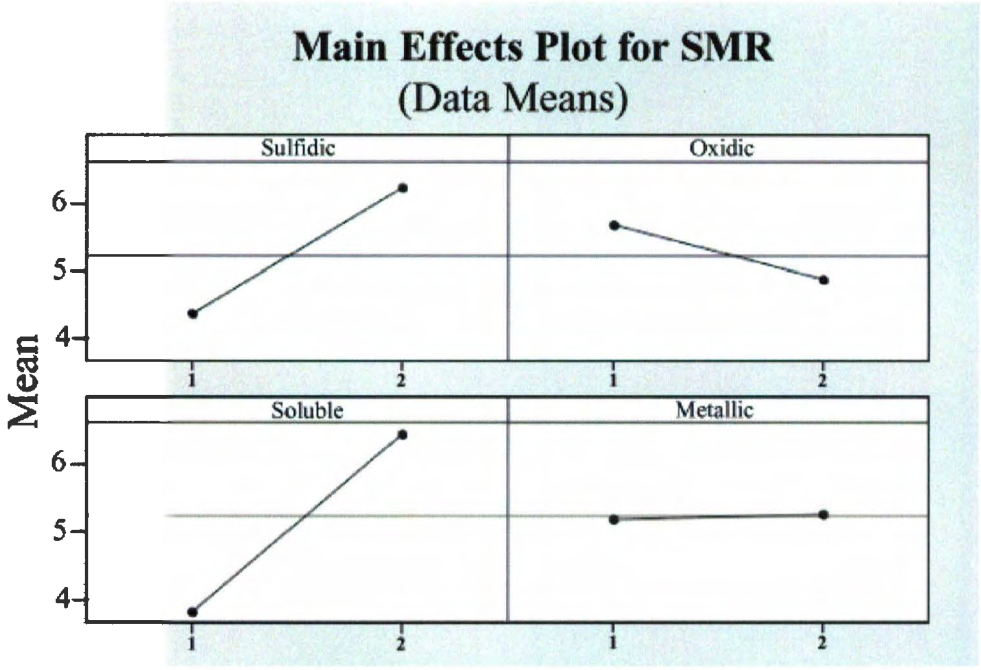

Figure 4.6: Main effect plot of exposure variables

4.4.3 Quantification of exposure

Any kind of exposure assessment needs quantification of the exposure dose or to which the people are exposed. The exposure dose has been calculated both for cancer and non cancer effect of maximum exposure level using the following equation;

$$ED = \frac{C * IR * EF}{BW} \tag{4.4}$$

where, ED, exposure dose, C concentration, IR inhalation rate, EF, exposure factor and BW, body weight. The non-cancer exposure dose has been estimated for one year of exposure and cancer dose is for lifetime exposure. Table-4.12 gives the exposure dose for non-cancer effect and Table-4.13 shows the exposure dose for cancer effect. The assumed values for exposure parameters were taken from US EPA,1991 given in the appendix-A.

Table 4.12: Exposure dose for non-cancer effect

Chemical	Max. Concentration mg/m^3(ATSDR,2005)	Target organ	Exposure Dose $mg/kg/day*$
Soluble nickel ($NiSO_4.6H_2O$)	10	Lung	4.865
Nickel Subsulfide	15	Lung	7.298
Nickel Oxide	50	Lung	24.328
Soluble nickel ($NiSO)_4.6H_2O$)	10	Renal	4.865
Nickel Subsulfide	15	Renal	7.298
Nickel Oxide	50	Renal	24.328

*For 1 year of exposure

Assumptions for exposure dose calculation:

Body weight (BW)=75 kg;

Concentration (C)=maximum concentration;

Inhalation rate (IR)=$20m^3$/day*8hrs/day=$6.66m^3$/8hrs per day.

For non cancer effect,

$$EF = \frac{5days\ per\ week * 8hrs.\ per\ week * 50week\ per\ yr.}{1yr. * 365days} = 0.23 \tag{4.5}$$

And, for cancer effect,

$$EF = \frac{5days\ per\ week * 8hrs.\ per\ week * 50week\ per\ yr.}{70yrs. * 365days} = 3.26E-3 \tag{4.6}$$

4.5 Summary

This chapter depicted the past and present exposure scenerio, level of exposure and maximum daily exposure dose for the nickel compounds. The exposure variables represented the exposed concentration level for the nickel species and the risk has been characterized by the exposed dust particle levels and the standard mortality

Table 4.13: Exposure dose for cancer effect

Chemical	Max. Concentration mg/m^3(ATSDR,2005)	Target organ	Exposure Dose mg/kg/day*
Soluble nickel ($NiSO_4.6H_2O$)	10	Alveolar proliferations	0.0695
Nickel Subsulfide	15	Alveolar proliferations	0.1042
Nickel Oxide	50	Alveolar proliferations	0.3476
Soluble nickel ($NiSO_4.6H_2O$)	10	Adrenal proliferations	0.06953
Nickel Subsulfide	15	Adrenal proliferations	0.1042
Nickel Oxide	50	Adrenal proliferations	0.3476

*For a lifetime exposure

ratios. From this analysis, it can be sumarized that the health risk is higher from the insoluble forms of nickel for low level of nickel exposure whereas the soluble form can also be accountable in the case of high level of nickel exposure or concentration.

Chapter 5

Toxicity Assessment

5.1 Introduction

In order to ensure worker's health and safety, there has to be a recommended exposure level for every toxic substances. This safety assessment need toxicological data to derive the safe dose for workplace. Once hazard identification and exposure assessment are done the next step in risk assessment process is toxicity assessment which includes dose response modeling based on human or animal data. Safe dose and toxicity values are derived from the biologically based dose response models. Dose response models describe the adverse outcome from specific dose of toxins using mechanistic foundation and stochastic (probabilistic) process. The derivation of safe dose from dose response modeling sometimes has been the objective of the risk assessment for regulatory agencies.

Principle health effects are not only dependent on the toxicity of substances but also depend on the solubility, route of exposure and the amount of exposure. In present study, the nickel sulphate is soluble compound and whereas nickel oxide and nickel subsulfide are insoluble or less soluble. This chapter describes the process of deriving the safe dose and toxicity values for soluble and insoluble or less soluble nickel

Criteria (AIC).

Global Measurement of Fitness: The significance level or the P-value is 0.1. P-value greater than 0.1 indicated that the model fitted the data well and P-value of 1.0 is consider as a perfect fit.

Local Measurement of Fitness: Scaled residuals are considered to be an absolute value and less than 2.0. The scaled residuals should be near to the Benchmark Response (BMR) value.

Visual Interpretation: This also gives some idea about the high dose region and fitness of the low dose region.

BMDL Value: The lowest BMDL can be considered as the Point of Departure (POD) as conservation estimate.

Akaike Information Criteria (AIC): Models from same family and different family are compared. AIC choses the less complex model. The less the AIC value the better the fitness.

Figure 5.2 depicts the steps involved in deriving toxicity values and toxicity score for chemicals.

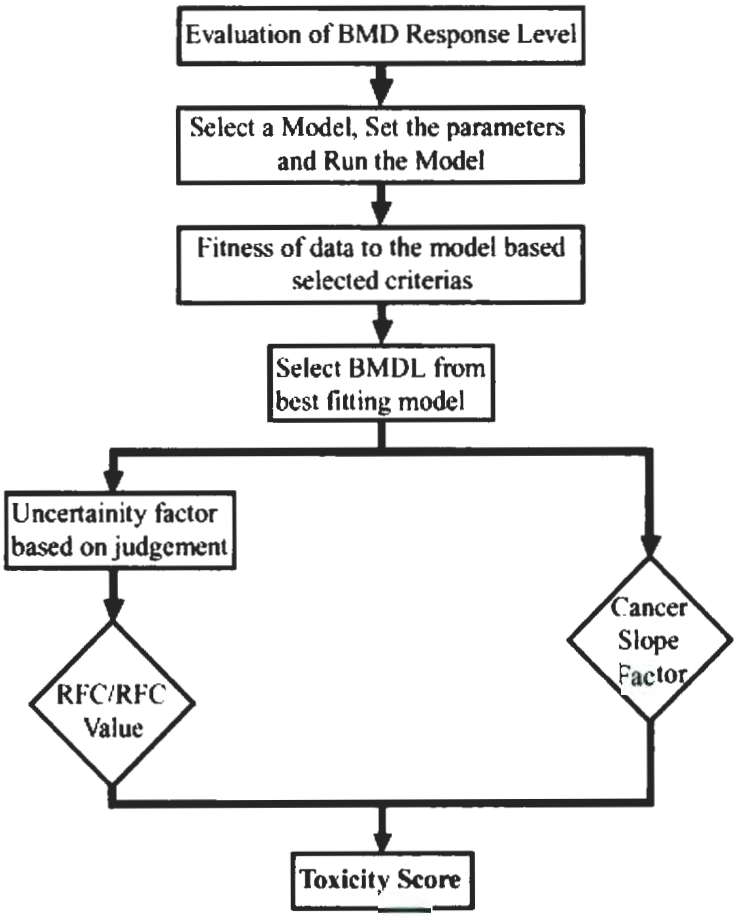

Figure 5.2: Steps involved in BMD approach

5.2 Comparison of BMD and NOAEL/LOAEL approach

Traditionally, threshold dose has been determined by the no observed adverse effect level or lowest observed effect level. In this approach, NOAEL or LOAEL are determined based on statistically significant response. This depends on the sample size and the selection of dose etc. NOAEL/LOAEL approach is relatively simple which does not consider the uncertainty related to dose response estimation. It might not give an accurate estimation for NOAEL as it focuses only on the data points which are

related to NOAEL or LOAEL and not on the entire data set. In contrast, in BMD approach the entire data set is fitted to mathematical models with specific benchmark response level. BMD approach also calculates the reference dose and slope factor. However, by reducing the uncertainty of traditional approach, it develops an occupational exposure level for workplaces. BMD approach uses 10% response level for non-carcinogenic and carcinogenic endpoints. The BMR level can be changed based on the risk assessment perspective.

5.3 Identification of critical effects based on chronic studies

For this analysis, four critical endpoints were selected based on toxicological chronic studies of nickel exposure. These are, death, renal effect, respiratory effect and cancer. For dose response modeling , the animal doses are usually used to assess the toxicological response. The animal doses can be converted to human dose through allometric formula (Ricci,2006). The allometric formula is presented in equation (5.1);

$$Human\ \ Dose = Animal\ \ Dose\langle\frac{Human\ \ Body\ \ Weight}{Animal\ \ Body\ \ Weight}\rangle^{\frac{1}{3}} \tag{5.1}$$

Homogeneity of the animal species is assumed in this formula. Four critical effects are discussed below for (1)soluble ,(2) sulfidic and (3)oxidic nickel exposure. Historically, chronic exposure to soluble and insoluble nickel compounds in refinery cohorts resulted in mortality of workers. Most of the human studies have been focused on the occupational nickel exposure. The studies were concerned with the estimation of

standard mortality ratio from cancer , respiratory effects from exposure and analysis of toxicity of the nickel compounds (ATSDR,2005). There has been a significant association between respiratory and renal effects and the increased risk of non-malignant disease in cohorts of nickel exposed workers. Past studies show that the increased nickel level in urine and urinary bita- microglobulin level of refinery workers are significantly related to each other (ATSDR,2005). Epidemiological evidence examined the carcinogenic risk for workers involved in process facility by assessing the carcinogenic effects of nickel. The evidence show that the nickel exposure has elevated the risk of lung cancer (ASTDR,2005). Figure-5.3 compares the No Observed Adverse Level (NOAEL) of animal species with human. The human equivalent NOAELs are compared with rat and mouse. It is observed from the figure that the most sensitive species is mouse for all critical effects. Further, the graphs in Figure-5.3 show that the sensitivity of rat is comparable than mouse to human.

5.4 Reference dose calculation using BMDS

The reference doses (RfD) or the safe exposure level has been derived based on some experimental animal data taken from literature using BMDS dose response modeling. EPA recommended 10% response level was taken to model the non-cancer dose response data.

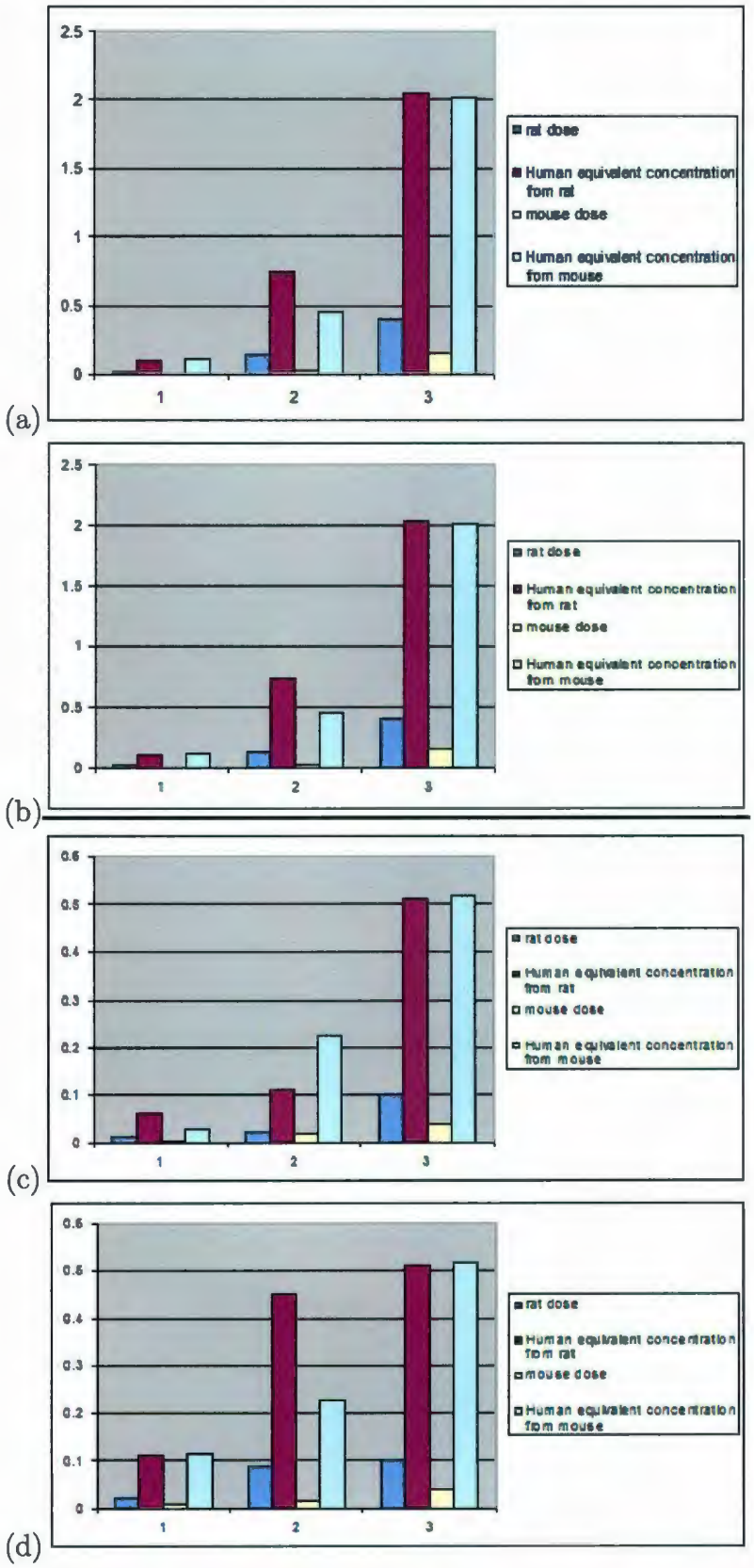

Figure 5.3: Identification of critical effects (a) death (b) renal effects (c) respiratory effects and (d) cancer

5.4.1 Comparative evaluation of Dose Response Models (DRMs)

The first step for deriving the Rfd is the comparative evaluation of dose response models based on the model fitness criteria for the data. The dichotomous models, weibull, gamma multi hit, log-probit, probit showed better fit to the data based on the selected criteria of BMD analysis. Comparative evaluation also considered the best fitted DRMs from the male and female rat dose response data.

Table 5.1: Selected dose response models after evaluation for non-cancer endpoint

Model	Chi-square	P-value	AIC	BMD	Chemical	Target organ
Weibull (power$\geq$ 1)	0.00	1.00	11.95	0.12	$NiSo_4.6H_2O$, (soluble)	respiratory
Weibull (power$\geq$ 1)	1.35	0.24	108.08	0.55	Nickel subsulfide, (insoluble)	respiratory
Gamma Multi hit	3.38	0.18	92.68	0.27	Nickel oxide (insoluble)	respiratory
Weibull (power$\geq$ 1)	0.64	0.72	96.084	1.44	$NiSo_4.6H_2O$, (soluble)	renal
Log-probit	0.03	0.86	134.96	0.13	Nickel subsulfide, (insoluble)	renal
Probit	1.21	0.54	296.56	0.63	Nickel oxide, (insoluble)	renal

5.4.2 Determination of Point of Departure (POD)

The 'Point of Departure' (POD) is the lowest limit of the observable range of doses. So, it is mainly described as the No Observed adverse effect level(NOAEL)/Lowest Observed adverse effect Level (LOAEL). For this study, the POD has been considered as the NOAEL. The table-5.2 shows the No observed adverse effect level for the chemicals at each critical endpoints.

Table 5.2: NOAEL for chemicals

Chemicals	Animal (rat) dose (mg/m^3) (ATSDR,2005)	Target organ	POD/NOAEL (mg/m^3)
$NiSo_4.6H_2O$, (Soluble)	0	Respiratory	0.11
	0.03		
	0.06		
	0.11		
Nickel subsulfide (insoluble)	0	Respiratory	0.27
	0.11		
	0.73		
Nickel oxide (insoluble)	0	Respiratory	0.17
	0.5		
	1		
	2		
$NiSo_4.6H_2O$, (Soluble)	0	Renal	0.11
	0.03		
	0.06		
	0.11		
Nickel subsulfide (insoluble)	0	Renal	0.10
	0.11		
	0.73		
Nickel oxide (insoluble)	0	Renal	0.37
	0.5		
	1		
	2		

5.4.3 Calculation of RfD

In the process of estimating 'Reference dose' (RfD), the determination of suitable uncertainty factor is an important consideration. ' The maximum uncertainty factor which EPA usually apply in RfD calculation is 3000. A default value of 10 is used for interspecies variability if information is limited about the animal to human extrapolation. Another 10 fold factor is used for the intra species or the extrapolation of sensitive to average population' (Zhao et al., 2006). The following equation has been

used to estimate RfD;

$$RFC = \frac{NOAEL}{UF * MF} \tag{5.2}$$

Table-5.3 shows the NOAEL, uncertainty factor and modifying factor used to calculate RfC/RfD for each critical effect. An uncertainty factor of 100 has been used for interspecies and intra species extrapolations.

Table 5.3: RfC for chemicals

Chemicals	POD/NOAEL (mg/m^3)	Critical Effect	Uncertainty Factor (UF)	Modifying Factor (MF)	RfC/RfD
$NiSo_4.6H_2O$, (Soluble)	0.11	Respiratory	100	10	1.12E-04
Nickel subsulfide (insoluble)	0.27	Respiratory	100	10	2.72E-04
Nickel oxide (insoluble)	0.17	Respiratory	100	10	1.71E-04
$NiSo_4.6H_2O$, (Soluble)	0.11	Renal	100	10	1.15E-04
Nickel subsulfide (insoluble)	0.10	Renal	100	10	1.00E-04
Nickel oxide (insoluble)	0.37	Renal	100	10	3.76E-04

5.4.4 Ranking of chemicals based on toxicity score

The toxicity score for the chemicals have been derived for each critical effect. The equation used to estimate toxicity score is given below;

$$Toxicity\ \ Score = \frac{Maximum\ \ Dose}{Reference\ \ Dose} \tag{5.3}$$

According to the toxicity score, the most harmful chemical in terms of non-cancer respiratory effect, has been nickel oxide. Table-5.4 shows the results derived for

toxicity scores of chemicals. The ranking is not much different for renal effect too. Nickel subsulfide is ranked as number 1 and nickel oxide as number 2 for adverse effect. Table-5.5 depicts the results for toxicity score for renal effect;

Table 5.4: Toxicity score of chemicals for respiratory effect

Chemicals	Max. Cont. (mg/m^3)	Critical Effect	RFC (mg/m^3)	Toxicity Score	Rank	Percent. to total score
$NiSo_4.6H_2O$, (Soluble)	10	Respiratory	1.12E-04	8.87E+04	2	20.4
Nickel subsulfide (insoluble)	15	Respiratory	2.72E-04	5.51E+04	3	12.67
Nickel oxide (insoluble)	50	Respiratory	1.71E-04	2.91E+05	1	66.92

Table 5.5: Toxicity score of chemicals for renal effect

Chemicals	Max. Cont. (mg/m^3)	Critical Effect	RFC (mg/m^3)	Toxicity Score	Rank	Percent. to total score
$NiSo_4.6H_2O$, (Soluble)	10	Renal	1.15E-04	8.66E+04	3	23.43
Nickel subsulfide (insoluble)	15	Renal	1.00E-04	1.50E+05	1	40.58
Nickel oxide (insoluble)	50	Renal	3.76E-04	1.33E+05	2	35.98

5.5 Cancer slope factor calculation by using BMDS

In order to derive the Cancer Slope Factor (CSF) for each chemical, the data were run applying the multistage cancer model using Benchmark Dose software (BMDS). The Multistage cancer model fits the data well at the low doses. The Benchmark Response Level (BMR) has been taken as 1 percent for cancer risk because the slope factor is assumed given between 0 percent to 1 percent.

5.5.1 Comparative evaluation of Dose Response Models (DRMs)

A comparative evaluation was done for selecting the best fitted model. The multistage cancer model was run for 1st, 2nd and 3rd degree of polynomial to choose the best fitted model to the data for both alveolar and adrenal proliferations. Before fitting the data to the model the animal dose was converted to human equivalent dose using the allometric formula (equation 5.1). The table for selected DRM has been depicted below;

Table 5.6: DRM for cancer slope factor

Model	Chi-square	P-value	AIC	BMD	Chemicals	Critical Effect
Multi hit (degree=3)	0.18	0.98	12.29	0.11	$NiSo_4.6H_2O$, (Soluble)	Alveolar proliferation
Multi hit (degree=2)	5.18	0.02	100.37	0.04	Ni subsulfide, (insoluble)	Alveolar proliferation
Multi hit (degree=3)	3.37	0.18	92.68	0.33	Nickel oxide (insoluble)	Alveolar proliferation
Multi hit (degree=2)	0.64	0.72	96.08	0.16	$NiSo_4.6H_2O$ (Soluble)	Adrenal proliferation
Multistage (degree=2)	4.59	0.03	194.8	0.008	Ni subsulfide, (insoluble)	Adrenal proliferation
Multi hit (degree=3)	0.28	0.86	295.64	0.89	Nickel oxide (insoluble)	Adrenal proliferation

5.5.2 Determination of cancer slope factor

Cancer slope factor can be described as the unit cancer risk from the risk agent. Comparative evaluation of DRMs is done to select the best fitted model from male and female rat's dose response data. Table-5.6 shows the results from the BMD analysis for cancer slope factor. It is noticed from the Table-5.7 that the unit cancer

risk is high from the nickel subsulfide both for alveolar and adrenal proliferations.

Table 5.7: Cancer slope factor for chemicals

Chemicals	Animal dose (mg/m^3) (ATSDR,2005)	Human equivalent dose ($mg/kg/day$)	Critical Effect	Cancer Slope Factor$(mg/kg/day)^{-1}$
$NiSo_4.6H_2O$,	0	0	Alveolar	0.236
(Soluble)	0.03	0.036	proliferation	
	0.06	0.072		
	0.11	0.132		
Ni subsulfide,	0	0	Alveolar	0.397
(insoluble)	0.11	0.17	proliferation	
	0.73	1.12		
Nickel oxide,	0	0	Alveolar	0.057
(insoluble)	0.11	0.17	proliferation	
	0.5	0.76		
	1	1.53		
	2	3.06		
$NiSo_4.6H_2O$,	0	0	Adrenal	0.710
(Soluble)	0.03	0.036	proliferation	
	0.06	0.072		
	0.11	0.132		
Ni subsulfide,	0	0	Adrenal	1.692
(insoluble)	0.11	0.17	proliferation	
	0.73	1.12		
Nickel oxide,	0	0	Adrenal	0.197
(insoluble)	0.5	0.76	proliferation	
	1	1.53		
	2	3.06		

5.5.3 Ranking of chemicals based on toxicity score

The ranking of chemicals was done by the Toxicity Score calculated. The equation (5.4) is given for calculation of Toxicity Score;

$$Toxicity\ \ Score = CSF * Maximun\ \ dose \tag{5.4}$$

Here, the CSF is the Cancer Slope Factor. Table-5.8 and 5.9 show that the ranking is high for the insoluble nickel forms. The percentage contribution to total score is more than 50 percent for nickel subsulfide and ranked as number 1 in the chemicals for both alveolar and adrenal proliferations. Nickel oxide is ranked as number 2 for both of the endpoints.

Table 5.8: Toxicity score for chemicals for alveolar proliferations

Chemicals	Critical Effect	Cancer Slope Factor$(mg/kg/day)^{-1}$	Toxicity Score	Rank	Percentage to Total Score
$NiSo_4.6H_2O$, (Soluble)	Alveolar proliferation	0.236	16.28	3	21.14
Ni subsulfide (insoluble)	Alveolar proliferation	0.397	39.7	1	53.34
Nickel oxide (insoluble)	Alveolar proliferation	0.057	19.95	2	25.53

Table 5.9: Toxicity score for chemicals for adrenal proliferations

Chemicals	Critical Effect	Cancer Slope Factor$(mg/kg/day)^{-1}$	Toxicity Score	Rank	Percentage to Total Score
$NiSo_4.6H_2O$, (Soluble)	Adrenal proliferation	0.710	48.99	3	16.77
Ni subsulfide (insoluble)	Adrenal proliferation	1.692	169	1	59.95
Nickel oxide (insoluble)	Adrenal proliferation	0.197	68.95	2	23.27

5.6 Setting of Occupational Exposure Level (OEL)

For a long term low dose exposure, the derivation of No Observed Adverse Effect Level (NOAEL) can be useful to define the Acceptable Daily Intake (ADI) for toxic

chemicals. Historically, regulatory agencies considered conventional approach to declare the threshold of toxicity for a chemical. This approach includes NOAEL values from different chronic studies and uncertainty factor to describe the Acceptable Daily Intake (ADI) or the safe level of exposure. In BMD approach, the threshold value is derived from more scientific dose response modeling . This has been a practical way of deriving the safe exposure level. In this analysis, it is assumed that the BMD calculated from 10% increased risk is comparable to the NOAEL (Galli et al. 2008). However, the BMD10 has been derived for the nickel workplace and recommended as the safe exposure level for chemicals. Table-5.10 describes the recommended safe dose/acceptable daily intake or the threshold value of toxicity for chemicals along with their critical effect.

Table 5.10: Acceptable daily intake for chemicals

Chemicals	Critical Effect	ADI/Safe dose/Safe Concentration (mg/m^3)
$NiSo_4.6H_2O, (soluble)$	Respiratory	1.12E-04
Ni subsulfide, (insoluble)	Respiratory	2.72E-04
Nickel oxide,(insoluble)	Respiratory	1.71E-04
$NiSo_4.6H_2O, (soluble)$	Renal	1.15E-04
Ni subsulfide, (insoluble)	Renal	1.00E-04
Nickel oxide,(insoluble)	Renal	3.76E-04

Chapter 6

Risk Characterization and Uncertainty Analysis

6.1 Introduction

This chapter deals with the characterization and evaluation of the risk of the exposed population. Risk characterization has been carried out using probabilistic approach. Probabilistic approach quantifies risk considering the uncertainties related to exposure estimates. The analysis involves uncertainty and variability in input parameters. Variability can be defined as the heterogeneity in the exposure parameters and uncertainty refers to the lack of knowledge about the parameter. However,Probabilistic Risk Assessment (PRA) determines the sources of uncertainty in risk quantification in order to obtain more data in related area.

There have been several numerical simulation methods for the propagation of moments or distribution of model inputs. The commonly used numerical methods are; Monte Carlo simulation and Latin Hypercube sampling (LHS). Monte Carlo simulation performs same calculation repeatedly for different values of input parameters. The input parameters are defined by the Probability Density Function (PDF) or probability models. The Latin Hypercube sampling of Monte Carlo simulation includes

sampling of input variables by dividing it into ranges of equal probabilities from Cumulative Density Function (CDF). It divides CDF into equal intervals, selects median from each interval and then performs the simulation repeatedly. In LHS, the values taken from the distribution are proportional to the probability density of the distribution (Cullen and Frey,1999). LHS is more reliable method than random Monte Carlo simulation because the statistical fluctuation is less in this method. Experiments showed that LHS allows more accurate representation of CDF when the sample size is small (Cullen and Frey,1999).

The U.S. EPA has issued some criteria for Monte Carlo analysis which has been reproduced below (U.S. EPA,1997);

- The purpose and scope of the assessment should be clearly articulated in a problem formulation section.
- The methods used for the analysis (including models, data and assumptions) should be clearly documented and easily located in the report.
- The results of sensitivity analysis should be presented and discussed in the report.
- The presence or absence of moderate to strong correlations and dependencies between the input variables should be discussed and accounted for, along with the effect these have on the output distribution.

- Tabular and graphical representation of the distributions of input and output including statistics and percentiles of special interest should be provided. Variability and uncertainty should be differentiated.

- The numerical stability of the central tendency and higher end (i.e., tail) of the output distribution should be investigated and discussed.

- Deterministic calculations should be provided for comparison with Monte Carlo output.

- The consistency and appropriateness of the metric used for the exposure estimates and that of available toxicity information, should be discussed.

6.2 Risk characterization

Probabilistic approaches for risk characterization involves two types of interpretation of probability. This includes; frequentest view of probability and subjective or Bayesian view of probability. The frequentest or conventional approach interprets the risk with probability distribution that is dependent on the dataset. This is an empirical approach of deriving risk where the data needs to be collected in random order from a population. The probability distribution with parameters are taken from this sample dataset. But in absence of data it is not possible to have a probability distribution for the parameters. In contrast, the event occurrence can be taken from prior knowledge, data and expert judgment in Bayesian approach. This approach is more appropriate when data are limited and gives a better estimate than the conventional

approach in absence of data. However, the classical theory of probability is based on random phenomena and in Bayesian theory, the event occurrence can be considered as more general or dependent on certain conditions.

Bayesian approach can create prior distribution based on currently available data for unknown parameters of risk model. The prior distribution is then updated using subsequently collected data and the likelihood function is taken based on assumptions. The updated distribution is called posterior distribution which reduces the uncertainty related to the new data.

The unknown parameter in risk model can be quantified by deriving the posterior density function for the parameter using Bayes theorem. Bayes theorem can easily be applied for continuous random variable. If x and y be the continuous random variables, then the Bayes theorem can be expressed as;

$$p(x/y,c) \propto p(x/c) * p(y/x,c) \tag{6.1}$$

Here, $p(x/c)$ is the prior density function containing the prior information about the parameter. The $p(x/y,c)$ is the posterior density function representing the current information about the parameter. The $p(y/x,c)$ is the likelihood function which relates x and y with the available information. The prior density can be taken from the same class of distribution from posterior density when the information is limited. This is called conjugate prior. The posterior expected values or moments for the

distribution can be derived by integrating the values for unknown parameter x along with the posterior density function.

6.2.1 Development of the risk model

The development of risk model has been done in four steps. First, the risk was estimated using deterministic approach and then the prior distribution for risk was derived using Monte Carlo simulation of Latin hypercube sampling method. Finally, the posterior distribution for risk was derived using Bayesian Monte Carlo analysis. The unknown input parameters or the exposure for probabilistic approach have been taken as uniformly distributed random variable within a minimum and maximum concentration level of past and present exposure data. The likelihood remained same for past and present exposure for the analysis. The posterior distribution ($g(\mu/data)$) is the product of the prior distribution ($g(\mu)$) and the likelihood of the exposure. Finally, the posterior normal distribution is derived from uniform prior as this is the conjugate prior. The posterior normal mean (m) and Standard Deviation (s) have been estimated based on the following formula;

$$m = \int \mu g(\mu/data) d\mu \tag{6.2}$$

And

$$s^2 = \int (\mu - m) 2 g(\mu/data) d\mu \tag{6.3}$$

For the posterior normal distribution, the values are assumed to be non negative and μ is the current mean exposure. And finally, the posterior risk has been estimated

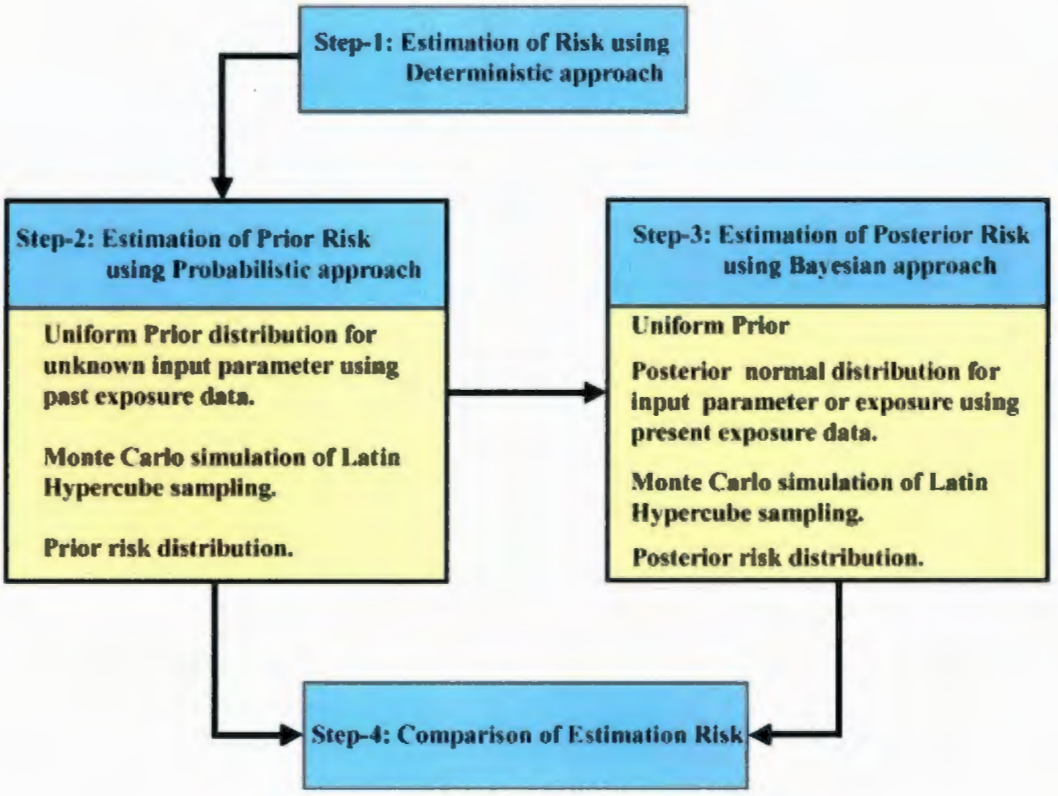

Figure 6.1: Steps involved in developing Risk model

using Monte Carlo Simulation of Latin hypercube sampling for the estimated posterior normal distribution for concentration by subjectively truncated from minimum-maximum value (0,max). This has repeatedly drawn positive values for risk from the distribution. The flow diagram in figure- 6.1 depicts the steps involved in development of risk model.

6.2.2 Risk estimation and comparison of estimated risk

The cancer and non-cancer risk estimation has been carried out using U.S. EPA recommended risk equations. The unknown input parameters in the risk equations were quantified using available data. From the past exposure data, the probability

distribution of concentration was provided using halfway substitution method from given maximum concentration. The posterior normal distribution for the concentration were derived for Soluble nickel: normal (mean=2.3E-7, st.d=7.7E-5), Nickel subsulfide: normal (mean=0.001, st.d=0.02) and nickel oxide: normal (mean=0.001, st.d=0.029). Before the analysis, the distribution or assumed values for the parameters were gathered. The values of other parameters were assumed based on U.S. EPA standards. It has been assumed that there is no correlation between the input parameters for the simplicity of the analysis. The Exposure factor has been calculated for one year (365 days) of exposure for non-cancer risk and for lifetime exposure of cancer risk. The Estimated Exposure Dose were calculated using the following equation;

$$EED = \frac{C * IR * EF}{BW} \tag{6.4}$$

In the equation-6.4, EED refers to the Estimated Exposure Dose, C, concentration or exposure, IR is Inhalation Rate, EF is Exposure Factor, and BW is Body Weight. The process of risk quantification is depicted in section 6.2.2.1 and 6.2.2.2.

6.2.2.1 Non-cancer risk

The following risk equations were used to calculate the non-cancer risk or Hazard Index (HI);

$$HI = \frac{EED}{RfD} \tag{6.5}$$

In equation-6.5, the HI is Hazard Index, RfD is the Reference Dose which was

Table 6.1: Input parameters for non-cancer risk quantification

Variable	Value	Unit	Parameter		Type of distribution
			Mean	ST.D	
Concentration of Soluble nickel	5-10 (min.-max.)	mg/m^3	7.5	2.582	Uniform
Concentration of Nickel subsulfide	7.5-15 (min.-max.)	mg/m^3	11.25	3.873	Uniform
Concentration of Nickel oxide	25-50 (min.-max.)	mg/m^3	37.5	12.91	Uniform
Inhalation Rate (IR)	6.66 (min.-max.)	$m^3/8hrs/day$	NA	NA	Assumed value
Exposure factor(EF)	0.23	NA	NA	NA	Assumed value
Body Weight(BW)	75	kg	NA	NA	Assumed value

derived in chapter 5 for the chemicals. The input parameters, values,units and probability models used for the estimation of risks are given in the Table-6.1. The HI

Table 6.2: Comparison of prior and posterior non-cancer risk for chemicals

Chemical	Target organ	Risk (Deterministic approach)	Prior risk (95% Confidence Interval)	Prior risk* Evaluation	Posterior risk (95% Credible Interval)	Posterior risk* Evaluation
Soluble	Lung	2.79E-01	0.19 - 0.36	Acceptable	0.007 - 0.034	Acceptable
Sulfidic	Lung	1.73E-01	0.12 - 0.23	Acceptable	7.7E-4 - 0.014	Acceptable
Oxidic	Lung	9.16E-01	0.63 - 1.21	Not Acceptable	0.004 - 0.2	Acceptable
Soluble	Renal	2.72E-01	0.18 - 0.36	Acceptable	0.007 - 0.03	Acceptable
Sulfidic	Renal	4.72E-01	0.32 - 0.62	Acceptable	0.002 - 0.036	Acceptable
Oxidic	Renal	4.18E-01	0.28 - 0.55	Acceptable	0.002 - 0.087	Acceptable

**HI is very high as the acceptable limit is <1

value for each chemical were estimated using deterministic and probabilistic approach and the risks were compared based on acceptance criteria. Non- cancer risks were calculated for two different target organs for their toxicity values. For respiratory effect, it has been assumed that the chemicals are deposited 100% of the calculated intake and for renal effect the 35% of dose is deposited into the target organ.

From this analysis , it has been depicted that the non-cancer risk level is within the

acceptable limit for the chemicals except the prior risk value for respiratory effect which is predicted high for the nickel oxide and about 75th, 90th and 95th percentiles are showing above the acceptable risk level. Table-6.2 and 6.3 describes the values for estimated prior and posterior non-cancer risks and percentile values of risk for chemicals respectively;

Table 6.3: Prior non-cancer respiratory risk for nickel oxide

Chemical	Target Organ	50th percentile value for risk	75th percentile value for risk	90th percentile value for risk	95th percentile value for risk
Nickel oxide	Lung	0.91	1.06	1.16	1.19

6.2.2.2 Cancer risk

The process for deriving risk has been same for both cancer and non-cancer effect. Here, the EF is considered for lifetime exposure in the calculation. The following risk equation is used to calculate the cancer risk;

$$Cancer \quad Risk = EED * CSF \tag{6.6}$$

The results show that the prior risk for all chemicals are above the acceptable limit and the posterior risk has been predicted high from the insoluble forms of nickel. The 50th, 90th and 95th percentiles show that the population is within the unacceptable region of prior risk. Again,it is seen that 90th and 95th percentile values for posterior lung cancer risk from nickel subsulfide are within an unacceptable range. However, for renal effect, the risks are predicted higher compared to the respiratory effect. The

Table 6.4: Input parameters for cancer risk quantification

Variable	Value	Unit	Parameter		Type of distribution*
			Mean	ST.D	
Concentration of Soluble nickel	5-10 (min.-max.)	mg/m^3	7.5	2.582	Uniform
Concentration of Nickel subsulfide	7.5-15 (min.-max.)	mg/m^3	11.25	3.873	Uniform
Concentration of Nickel oxide	25-50 (min.-max.)	mg/m^3	37.5	12.91	Uniform
Inhalation Rate (IR)	6.66 (min.-max.)	$m^3/8hrs/day$	NA	NA	Assumed value
Exposure factor(EF)	3.26E-3	NA	NA	NA	Assumed value
Body Weight(BW)	75	kg	NA	NA	Assumed value

*The uniform distribution has been taken from the halfway substitution method from given maximum concentration.

*$CSF\ (mg/kg/day)^{-1}$ derived from chapter 5 and $EED(mg/kg/day)$ derived from chapter 4.

25th, 50th, 75th, 90th and 95th percentiles are higher than the acceptable level for exposure to nickel subsulfide. The 90th and 95th percentiles are higher for nickel oxide exposure. This means that about 90-95 percent of observation will be equal or below the acceptable range which again violates the acceptable criteria for risk. The results were presented in Table-6.5, 6.6, 6.7 and 6.8. [ht] [ht]

Table 6.5: Comparison of prior and posterior cancer risk for chemicals

Chemical	Target organ	Risk (Deterministic approach)	Prior risk (95% Confidence Interval)	Prior risk* Evaluation	Posterior risk (95% Credible Interval)	Posterior risk* Evaluation
Soluble	Lung	5.1E-4	3.5E-4 - 6.7E-4	Not acceptable	5.78E-11 - 4.13E-9	Acceptable
Sulfidic	Lung	1.2E-3	8.85E-4 - 1.7E-3	Not acceptable	2.62E-8 - 1.8E-6	Not acceptable
Oxidic	Lung	6.2E-4	4.2E-4 - 8.1E-4	Not acceptable	5.49E-9 - 3.82E-7	Acceptable
Soluble	Renal	1.54E-3	1E-3 - 2E-3	Not acceptable	1.73E-10 - 1.24E-8	Acceptable
Sulfidic	Renal	5.5E-3	3.7E-3 - 7.2E-3	Not acceptable	1.1E-7 - 7.8E-6	Not acceptable
Oxidic	Renal	2.1E-3	1.5E-3 - 2.8E-3	Not acceptable	1.8E-8 - 1.32E-6	Not acceptable

**Acceptable Cancer risk is $<1*10^{-6}$.

Table 6.6: Prior cancer risk for chemicals

Chemical	Target Organ	90th percentile value for risk	50th percentile value for risk	95th percentile value for risk
Soluble Nickel	Lung	6.49E-04	5.12E-04	6.66E-04
Nickel subsulfide	Lung	1.63E-03	1.29E-03	1.68E-03
Nickel oxide	Lung	7.83E-04	6.18E-04	8.04E-04
Soluble Nickel	Renal	1.95E-03	1.54E-03	2.00E-03
Nickel subsulfide	Renal	6.97E-03	5.51E-03	7.16E-03
Nickel oxide	Renal	2.70E-03	2.13E-03	2.78E-03

Table 6.7: Percentile values for posterior lung cancer risk

Percentile value for risk	Posterior risk value for nickel subsulfide
5%	5.25E-08
25%	2.65E-07
50%	5.58E-07
75%	9.47E-07
90%	1.34E-06
95%	1.60E-06

Table 6.8: Percentile values for posterior cancer risk for renal effect

Percentile value for risk	Posterior risk value for Nickel subsulfide	Posterior risk value for Nickel oxide
5%	2.23E-07	3.78E-08
25%	1.13E-06	1.91E-07
50%	2.38E-06	4.02E-07
75%	4.03E-06	6.82E-07
90%	5.74E-06	9.72E-07
95%	6.83E-06	1.15E-06

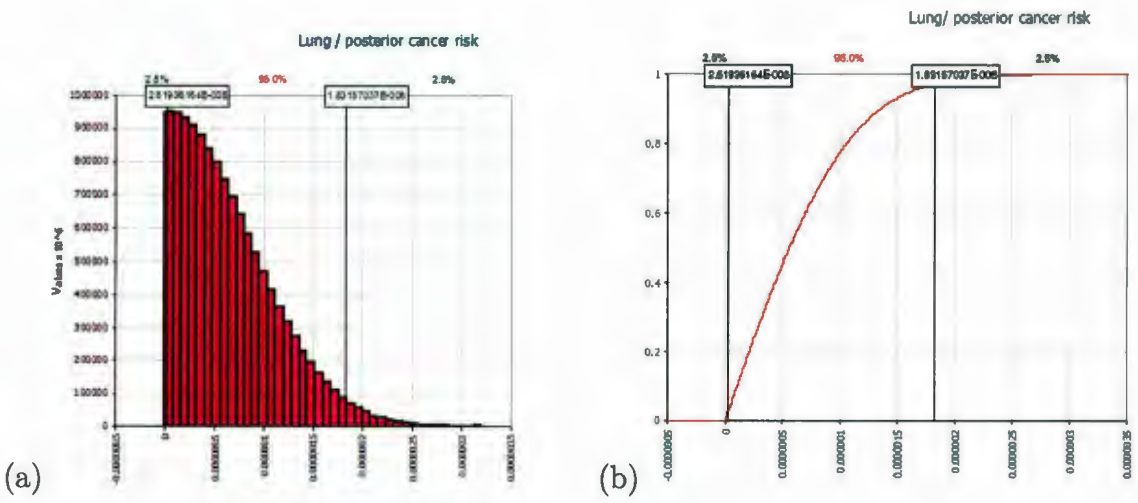

Figure 6.2: Posterior lung cancer risk from nickel subsulfide (a) PDF (b) CDF

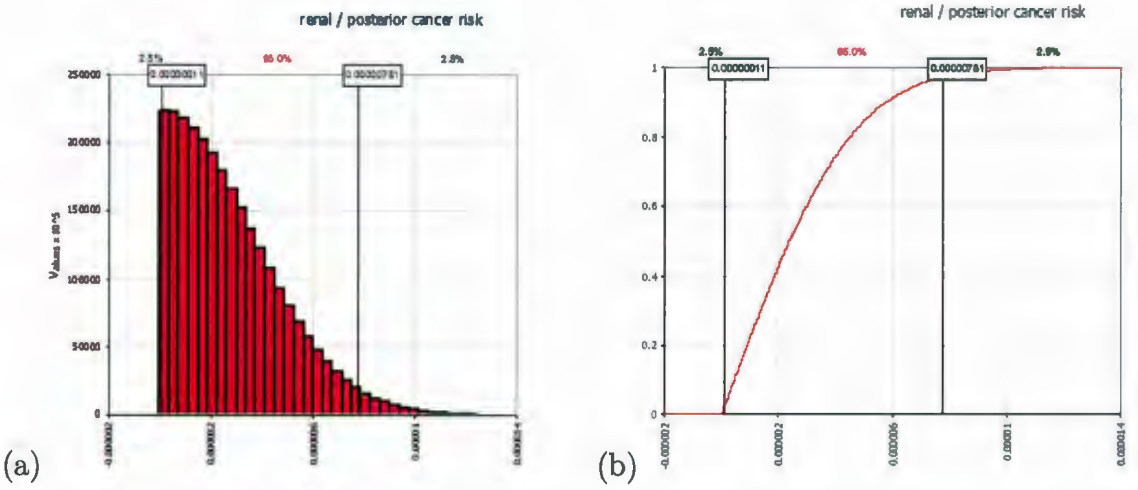

Figure 6.3: Posterior cancer risk from renal effect for nickel subsulfide (a) PDF (b) CDF

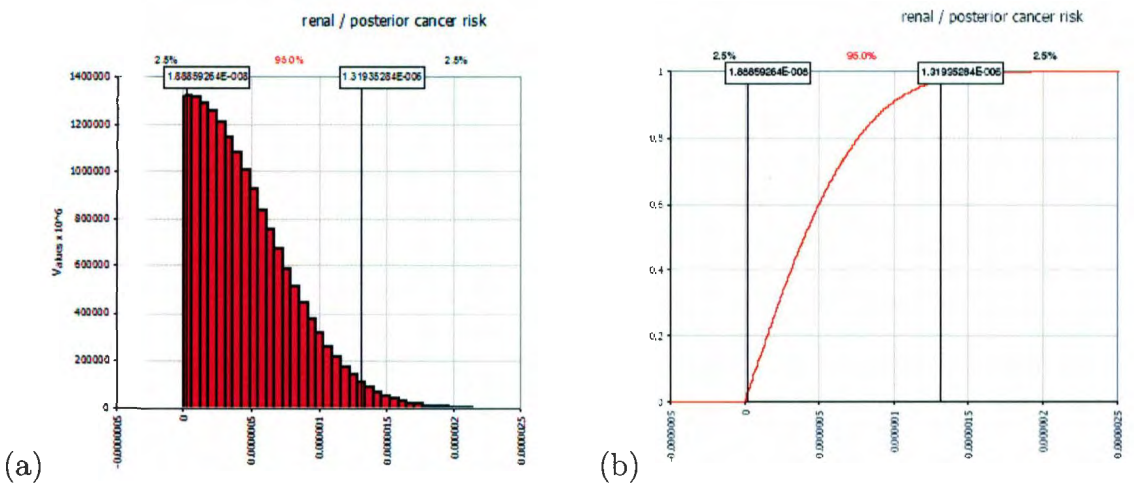

Figure 6.4: Posterior cancer risk from renal effect for nickel oxide (a) PDF (b) CDF

Chapter 7

Sensitivity Analysis

7.1 Introduction

Sensitivity analysis can be classified into two classes; deterministic analysis and probabilistic analysis. Probabilistic analysis involves statistical methods for sensitivity analysis of exposure parameters. This is done by running simulation for each input in relation to output. Distributions are assigned to the parameters and run the simulations. Simulations can be run using techniques, like, Monte Carlo simulation, Latin hypercube sampling and some other common methods. The examples of statistical method include, regression analysis, analysis of variances, response surface methods, Fourier amplitude sensitivity test, and mutual information index (Frey and Patil, 2002). Regression analysis is a powerful tool for independent random samples. The input and output parameters can be compared using regression coefficients, standard error of regression coefficients and the level of significance of regression coefficient (Frey and Patil, 2002). Regression coefficients are ranked to identify the nominal range of sensitivity of input parameters to the output. Usually the values of the coefficients are ranged from -1 to 1.

This chapter deals with the sensitivity analysis of exposure parameters in risk quantification. Risk models often require sensitivity analysis to determine the important exposure parameters in order to mitigate the risk. This also plays a significant role in further study or data collection. In this chapter, the regression coefficients are used to relate importance of each input parameters with the output which helps evaluating the impact of input parameters on the output or the results.

7.2 Characterizing variability and uncertainty in exposure parameters

The probability models for exposure concentration were generated using bootstrap approach. Bootstrap method generates the empirical distribution from the original data set drawn at a random (with replacement) order. The steps involved in generating bootstrap probability model are; (*i*) arranging observed random sample in an ascending order; (*ii*) development of probability model based on observed data ; (*iii*) computation of bootstrap probability model from the number of independent samples (N); (*iv*) generation of sought statistics. Table 7.1 shows the statistics of probability distribution generated by bootstrap method. Probability distribution for

Table 7.1: Nickel refinery dust exposure (after replacement)

Variable	Mean	SE Mean	St. Dev	Minimum	Median	Maximum
Sulfidic	0.120	0.001	0.035	0.030	0.121	0.216
Oxidic	0.270	0.003	0.082	0.081	0.261	0.517
Soluble	0.026	0.0001	0.004	0.014	0.026	0.038

other exposure parameters were generated for sensitivity analysis mainly based on literatures. Table-7.2 shows the values considered for each input parameter.

Table 7.2: Input parameters for sensitivity analysis

Parameter	Description	Units	Distribution	Estimate	Reference
C	Concentration	mg/m^3	Normal	-	-
IR	Inhalation rate	m^3/day	Uniform	Min:5.04 Max:17.76	Dawoud& Purucker,(1996)
EF	Exposure frequency	$Days/yr$	Triangular	Min:180 Max:365 Most likely:345	Dawoud & Purucker,(1996)
ED	Exposure duration	$Year$	Uniform	Min:50 Max:70	Judgment
BW	Body weight	Kg	logNormal	G.Mean:4.34 G.St.dev:0.17	Dawoud & Purucker,(1996)
AT	Average time	$Days$	Uniform	Min:365 Max:1825	Judgment
RR	Retention rate	Dimension less	-	V1	-
ABS	Absorption factor	Dimension less	-	1	-
ET	Exposure time	$Days/yr$	Triangular	Min:5.7E-4 Max:1.4E-3 Most likely:9.1E-4	Judgment

7.3 Sensitivity analysis of exposure parameters by ranking

The sensitivity analysis has been done using Monte Carlo Simulation of Latin Hypercube Sampling method. First, the forms of nickel has been identified for generating dust (see chapter-4). The results in table-7.3 shows the sensitivity of output to its input variables (oxidic, soluble and sulfidic). The regression coefficients show the ranking of the variables. Nickel oxide has been ranked as number one for generating dust. The percentile plot (Figure-7.1) and the percentage change graph (Figure-7.2) depict that there is a sharp increase in dust level with the increase in oxidic nickel. Soluble nickel has little or no impact on the output. The tornado graph (Figure-7.3)

shows the exposure to oxidic nickel varies with the output more than the other exposure variables.

The sensitivity report shown in table-7.4 suggests that the average time of exposure

Table 7.3: Rank of input for dust exposure

Rank	Name	Description	Regression coefficient
1	Oxidic	Normal(0.269,0.0816)	0.882
2	Sulfidic	Normal(0.119,0.0352)	0.445
3	Soluble	Normal(0.0259,0.0043)	0.147

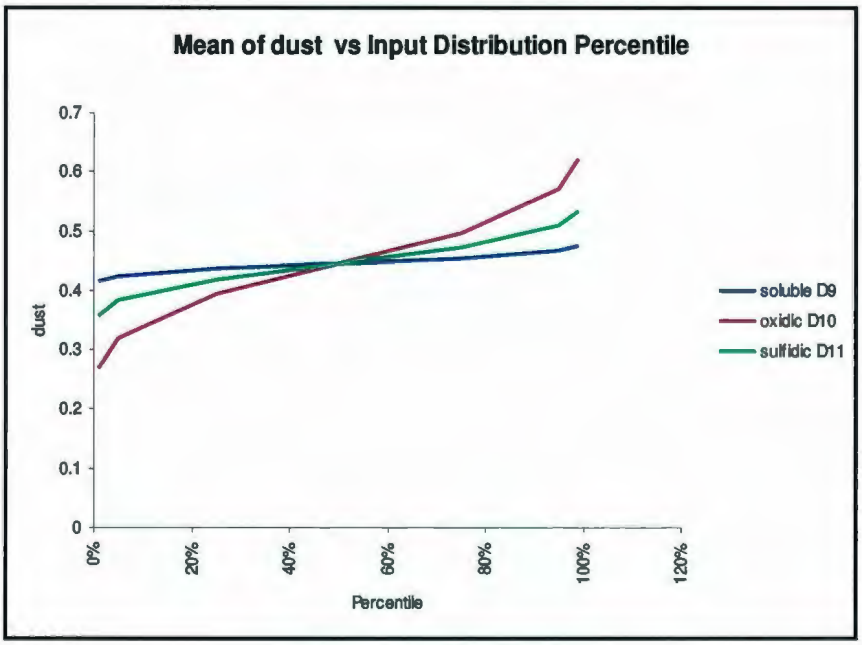

Figure 7.1: Percentile graph for dust exposure

and the level of exposure are the important parameters to be considered for cancer risk. The percentile graph (Figure-7.4) and the percentage change graph of cancer risk (Figure-7.5) shows that the exposure time and level of exposure are increasing with the increase in risk. The tornado graph (Figure-7.6) represents the variation of input with the output.

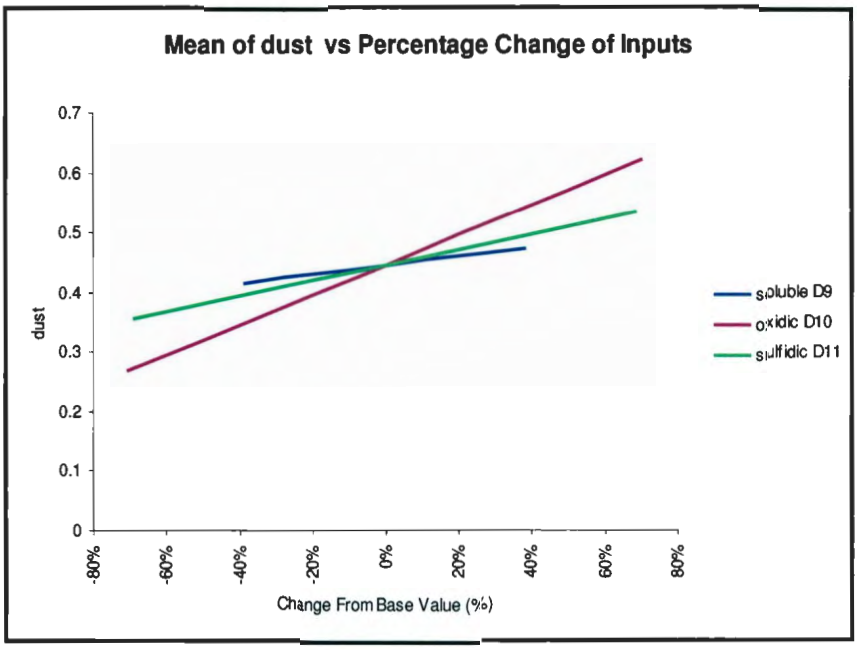

Figure 7.2: Percentage change graph for dust exposure

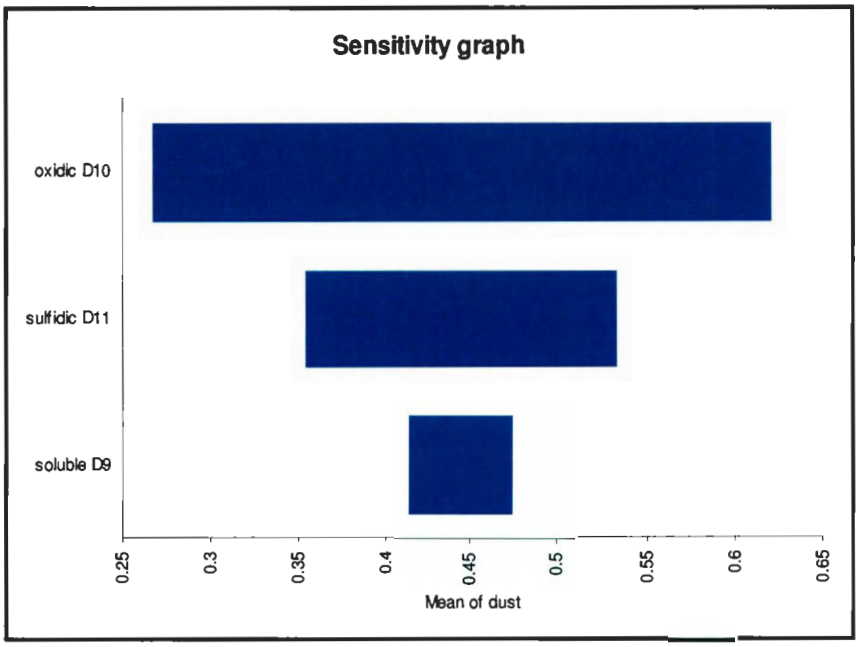

Figure 7.3: Tornado graph for dust exposure

Table 7.4: Rank of input for output cancer risk

Rank	Name	Description	Regression coefficient
1	Average time $(days)$	Uniform(365,1825)	-0.646
2	Oxidic(mg/m^3)	Normal(0.269,0.0186)	0.442
3	Exposure time $(days/yr)$	Triang(0.00057,0.00091,0.0014)	0.26
4	Body weight(kg)	Lognorm2(4.34,0.17)	-0.24
5	Exposure frequency$(days/yr)$	Triang(180,345,365)	0.209
6	Exposure duration$(year)$	Uniform(50,70)	0.151

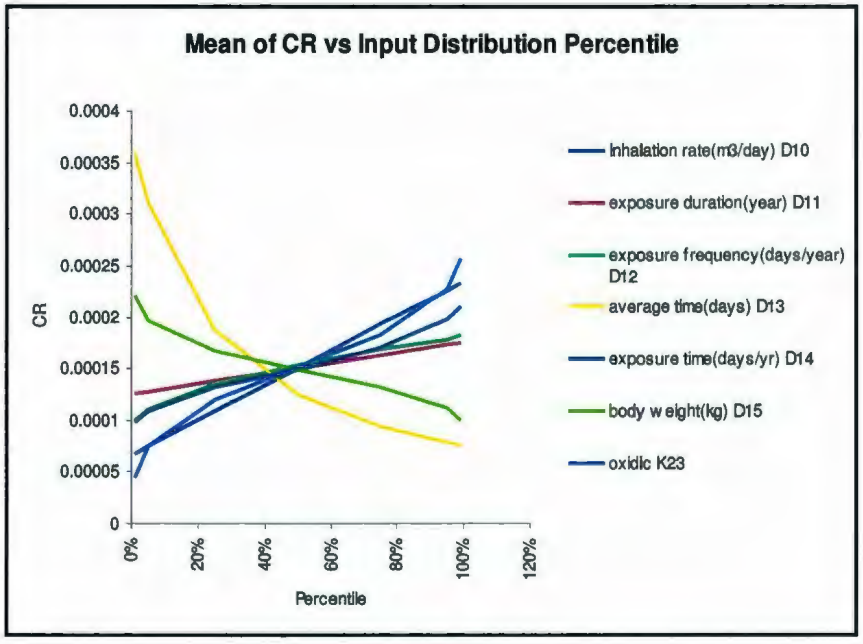

Figure 7.4: Percentile graph for cancer risk

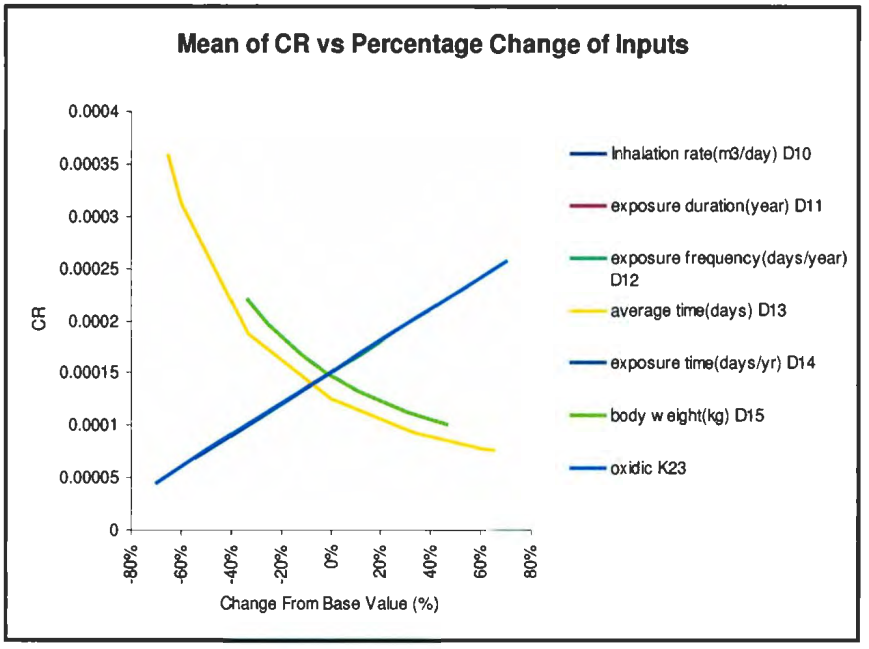

Figure 7.5: Percentage change graph for cancer risk

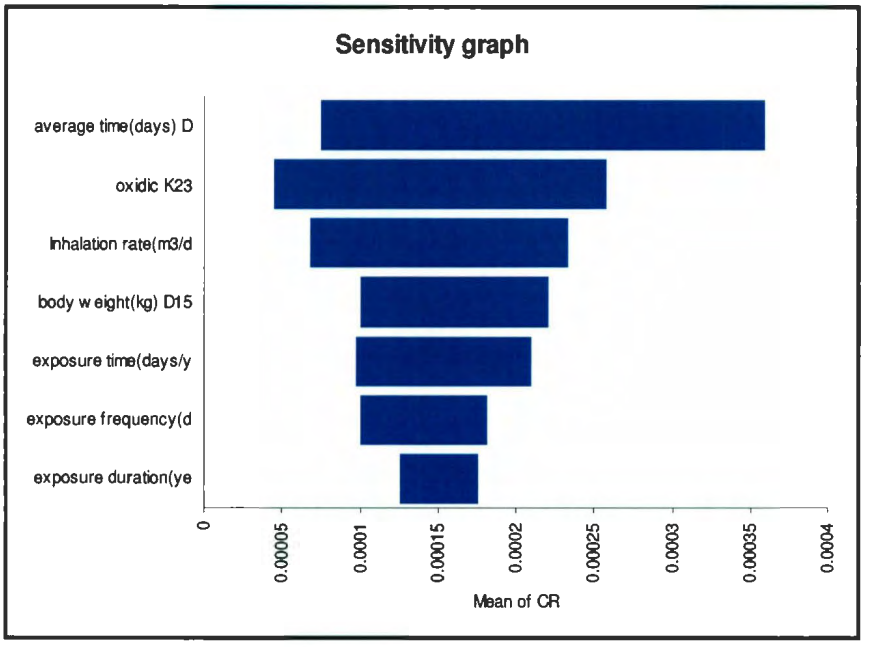

Figure 7.6: Tornado graph for cancer risk

Chapter 8

Conclusion and Recommendations

8.1 Summary and conclusion

Present approaches for Human Health Risk Assessment (HHRA) have been studied, discussed and a new approach for assessing human health risk for chemical exposure in process facility is proposed. Considerations have been given for high risk operations in process facility for occupational hazards from nickel exposure through inhalation. The risk assessment framework includes four steps; (*i*) hazard identification; (*ii*) Exposure-response analysis; (*iii*) Toxicity assessment; (*iv*) Risk characterization and uncertainty analysis. Hazards were identified based on the past evidence from literatures and secondary sources have been used to confirm identified hazards. First, occupational nickel exposure were analyzed using two established statistical methods to identify the significant exposure parameters related to risk. Multivariate analysis was used to assess the exposure and exposure response models were developed using regression analysis. In the next step, Benchmark Dose (BMD) analysis has been carried out to find out the toxicity values for nickel compounds and Occupational Exposure Level (OEL) in the workplace. BMD approach considered the entire dataset to derive the toxicity results for nickel compounds using dose response modeling. In

the risk characterization step, a probabilistic risk model is developed to quantify the health risk from the exposure to nickel compounds. The prior risk (risk from past exposure) was updated using Bayesian approach to derive posterior risk (risk from current exposure). And, finally, The developed risk models were applied in sensitivity analysis and discussed to identify the relative importance of the exposure parameters for the risk.

Historically, process facilities have been hazardous place to work with. Epidemiological evidence shows a clear view of occupational chemical exposure in process facility. Several case studies related to occupational nickel exposure have been carried out and published. Past exposure in nickel refinery showed an increased risk of lung cancer. Occupational diseases or cancer have been detected after prolong exposure to the compounds. The present study proposes risk model for nickel workplace exposure. The exposure to soluble and insoluble forms of nickel have been analyzed and the insoluble forms have been found more toxic in terms of both carcinogenic and non-carcinogenic responses. The results from epidemiological evidences and the toxicological assessment of nickel converged to same conclusion. The results from risk model showed that the risk from soluble form has been in an acceptable range. However, the cancer risks were predicted above acceptable range for workplace from the exposure to insoluble forms of nickel. The sensitivity report suggested that the exposure level (dose) and the exposure time have significant impact on the risk computations.

8.2 Recommendations

On the basis of present study, the following recommendations related to risk reduction and improvement in methodology of risk assessment have been suggested;

8.2.1 Recommendations related to risk reduction

- Regular air sampling and nickel speciation analysis should be done in high risk operations , like , high temperature operations and feed preparation.
- Special considerations should be given to high risk areas for dust control and ventilation in process facility.
- Routine health checkup for the exposed workers must be carried out in order to ensure worker health and safety.
- The number of workers should be minimized as far as possible in high risk areas.
- Appropriate design and control strategies should be taken into consideration to minimize the risk and release of carcinogens.
- Raising awareness of the workers about the safety issues.
- The recommended Occupational Exposure Limit (OEL) or the safe dose should be maintained and the exposure level should be minimized as far as possible or technologically feasible.

- Personal protective measures should be provided for the employees and enforced to be used in the working hours.

8.2.2 Recommendations related to future improvements in methodology

- More epidemiological studies need to be carried out to collect more relevant data in the area.
- Risk assessment data should be made more available to the risk assessors and managers.
- More scientific toxicological data are required in the area related to reliable animal experimentation.
- Approaches to qualitative risk assessment needs to be given more emphasis as the quantitative approaches required more accuracy and precision.
- Exposure scenarios needs to be described more elaborately describing the present workplace exposure.
- The workplace exposure data should be made more accessible for the researchers which will give more precise, accurate and validated risk assessment methodologies for Human Health Risk Assessment (HHRA) in process facility.

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Appendix A: The First appendix

A.1 Appendix: Data collection

A.1.1 Sources of data

The following secondary sources have been used to gather data for risk assessment;

1. Dawoud, E. A. and Purucker, S. T., February 1996, Quantitative Uncertainty Analysis of Superfund Residential Risk Pathway Models for Soil and Groundwater: White Paper, Environmental Restoration Risk Assessment Program, U.S. Department of Energy, Office of Environmental Management, 6-9.

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5. (ATSDR, 2005), Toxicological Profile for Nickel, August 2005, U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, 25-28, 47-58, 82-85, 88-89.

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Appendix B: The Second appendix

B.1 Appendix: Commands used for risk modeling and sensitivity analysis

B.1.1 Minitab commands

1. The following Minitab commands were used to derive the posterior density;

Random 2002 c1;[generates uniformly distributed random numbers]

Uniform min max.

Let c4=c2*c3 [gives g(μ/data); c2= g(μ); c3=likelihood]

Let c5=c1*c4 [gives μ *g(μ/data); c1= μ;]

%tintegral.mac c1 c5; Output k1 c6. [gives posterior mean]

Let c6=(c1-k1)**2*c4

%tintegral.mac c1 c6; Output k2 c7.[gives posterior variance]

Let k3=sqrt(k2)[gives posterior St.Dev.]

Print k1-k3.

2. The gmacro used for sensitivity analysis is given below;

gmacro

bootex1

```
do k1=1:999
sample 16 c1 c6;
replace
let c7(k1)=mean(c6)
sort c6 c8
enddo
let k2=c7(50)
let k3=c7(950)
print k2-k3
descr c7
endmacro
```