

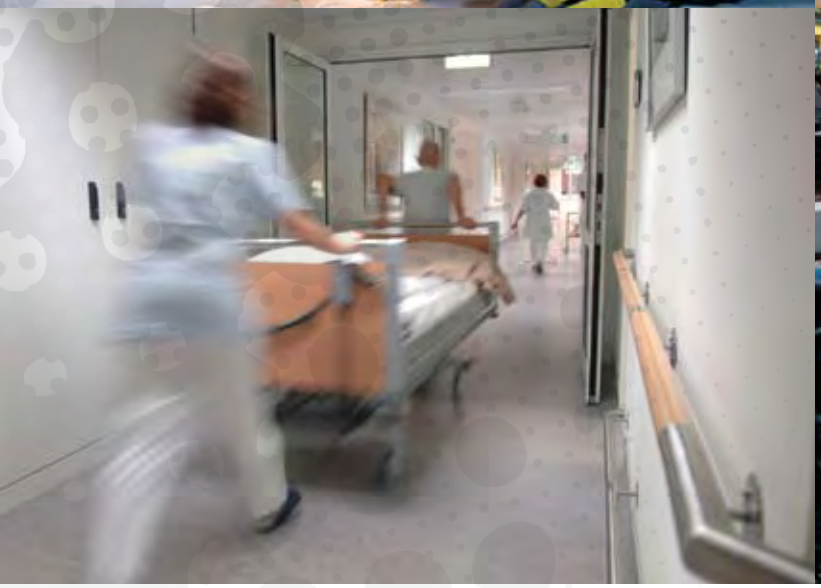


Cancer risk assessment for workers exposed to nitrosamines in a warehouse of finished rubber products in the Eastern Townships (Québec, Canada)

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Québec

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Direction des risques biologiques
et de la santé au travail

Direction de la santé environnementale
et de la toxicologie

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AUTHORS

Gaétan Carrier, Ing, MD, PhD, Medical Adviser
Direction des risques biologiques et de la santé au travail
Institut national de santé publique du Québec (Québec public health institute)

Marie-Claire Desrosiers, Bachelor in Biological Sciences, Master's trainee
Santé environnementale et santé au travail profil toxicologie
Université de Montréal

Georges Adib, MSc, Industrial hygienist
Direction des risques biologiques et de la santé au travail
Institut national de santé publique du Québec (Québec public health institute)

UNDER THE COORDINATION OF

Gaétan Carrier, Ing, MD, PhD, Medical Adviser
Direction des risques biologiques et de la santé au travail
Institut national de santé publique du Québec (Québec public health institute)

LAYOUT

Samia Abdelbaki
Direction des risques biologiques et de la santé au travail
Institut national de santé publique du Québec (Québec public health institute)

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FOREWORD

This risk analysis was undertaken in response to a request from Dr. Louise Soulière, director of public health and evaluation at the Agence de la santé et des services sociaux de l'Estrie, which she addressed to the Institut national de santé publique du Québec (INSPQ) (Québec public health institute). She sought the support of the INSPQ to assist the public health department in assessing the health risk associated with exposure to nitrosamines in a warehouse of finished rubber products in the Eastern Townships. The public health department was primarily concerned with the risk of cancer associated with exposure to nitrosamines. Indeed, the carcinogenic effects of nitrosamines present in this industry are clearly demonstrated in animals. In addition, these molecules are suspected of being carcinogenic to humans by several organizations, namely, the International Agency for Research on Cancer, Health Canada and the National Toxicology Program (NTP) of the United States.

In the Eastern Townships, in 2006, the industry of rubber products consisted of 30 factories employing about 3,500 workers. This would correspond to 30% of facilities and 50% of workers in this industry in the province of Québec (figures obtained from the provincial occupational health information system, SISAT, 2008). The rubber products factories established in the Eastern Townships specialize mainly in the manufacture of sealing strips for the automotive sector.

In her request, Dr. Soulière mentioned that in recent years, environmental assessments conducted by the occupational health team in five plants in the Eastern Townships indicated a significant exposure of workers to rubber fumes. N-nitrosodimethylamine (NDMA) was clearly predominant in most samples taken from these work environments. Concentrations up to 17 µg/m^3 of total nitrosamines were measured in ambient air of these factories in the workers' breathing zone.

Following these observations, several preventive measures (ventilation, adjustments of working methods, respiratory protection) have been implemented at various workstations in the production area. This was made possible through the cooperation of the industry, the Commission de la santé et de la sécurité du travail (CSST) (Québec's workman compensation board) and the regional occupational health teams. In most situations, these actions led to lowering the nitrosamines concentrations at levels below 1 µg/m^3 in the production area.

However, as far as workers' health was concerned, the emission of volatile nitrosamines from rubber products, mainly in the warehouse of finished goods lingered. This was a concern for the public health authority of the Eastern Townships. For instance, in 2006-2007, the average concentration of total nitrosamines in the workers' breathing zone in one large warehouse of finished rubber products was 2.7 µg/m^3, while the average concentration of NDMA was 2.2 µg/m^3.

Currently in Québec, there is no occupational exposure limits for these molecules. However, the *Règlement sur la santé et la sécurité du travail* (Québec's health and safety regulations), requires that exposure to NDMA be kept as minimum as possible as indicated by the notation "EM".

Thus, on the basis of risk estimates in the literature and standards established elsewhere in the world and the EM notation for NDMA in Québec regulations, the public health authority and the CSST of the Eastern Townships consider these results to be worrisome and worthy of further investigations, in a perspective of preventing a potential cancer risk in the long term. According to Dr. Soulière, it is likely that such a situation prevails in several warehouses of finished rubber products in the Eastern Townships and elsewhere in Québec. It is within this context that she sought the support of the INSPQ. Consequently, Dr. Maurice Poulin, scientific coordinator of the biological and occupational health hazards unit at the INSPQ gave us the mandate to conduct a risk analysis in collaboration with a regional working team under the responsibility of Dr. Louise Soulière.

SUMMARY

This risk assessment was undertaken at the request of Dr. Louise Soulière, director of public health and evaluation at the Agence de la santé et des services sociaux de l'Estrie.

The objective of this work is to assess whether workers in a warehouse of finished rubber products in the Eastern Townships are at risk of contracting cancer because of the presence of nitrosamines in the workplace ambient air and, in the case of a non-zero risk, to suggest a threshold limit not to be exceeded in order to make the risk negligible.

The methodology used involves estimating workers' exposure to nitrosamines in the warehouse; assessing the carcinogenic potential for humans of the main nitrosamine molecules found in that environment; estimating the dose-cancer excess relationship based on epidemiological studies published so far and estimating the cancer risk associated with such exposure. This will allow suggesting an occupational exposure limit aimed at preventing the type of cancers potentially attributable to such exposure.

Between 2005 and 2008, concentrations of total nitrosamines in various areas of the warehouse ranged from 0.74 to 11.43 µg/m³ with arithmetic means of 2.89 to 4.59 µg/m³, depending on the work stations or the targeted sites. Half of those concentrations were lower than 3.53 µg/m³, with an overall arithmetic mean of 3.95 µg/m³. Concentrations of N-nitrosodimethylamine (NDMA) represent about 80% of total nitrosamines. These levels are similar to those observed elsewhere in the world.

Research shows that many nitrosamines found in the work environment, including NDMA, are carcinogenic in animals. Carcinogenic effects were observed for oral and respiratory exposures. The type of cancer induced depends on the route of entrance. The incidence of cancer is based on the daily administration dose and duration of exposure.

The cancers would be initiated by some metabolites of nitrosamines activated by an oxidative mechanism, which have the power to produce mutations in DNA. Human cells metabolize nitrosamines in a manner similar to that of animal cells and nitrosamine metabolites produced in rodents are also produced in humans. It has been shown that several human tissues (liver, kidney, lung and brain) metabolize NDMA and that the same DNA-adducts as those observed in experimental animal studies are also detected in humans. Based on these observations, it is reasonable to anticipate that NDMA and other nitrosamines present in these workplaces are carcinogenic in humans.

In 1998, experts commissioned by the International Agency for Research on Cancer (IARC) indicated that in the rubber products industry, there was a sufficient degree of evidence of a causal relationship to be inferred for excess mortality from certain cancers observed in some cohorts of rubber workers. However, the lack of measured concentrations of contaminants in the workplace prevents drawing up a causal link with specific risk factors.

Furthermore, confounding factors potentially associated with the cancer types observed were only rarely controlled in these studies. A meta-analysis by Kogevinas et al. reached the same conclusion.

In 1990 in Germany, a significant epidemiological investigation was initiated to explore the cancer risk factors associated with this industry. This investigation led to the publication of five articles between 1996 and 2000, on the follow-up of a cohort of some 11,000 workers employed between 1910 and 1991 in five different facilities manufacturing various rubber products such as tires and gaskets used in automobiles and appliances.

Based on our analysis of these studies, we found that the threshold inducing an excess risk of mortality from cancers associated with exposure to nitrosamines for an average exposure period of approximately 10 years in the German cohort analyzed, corresponds to an average concentration between 2.5 µg/m^3 and 15 µg/m^3 of total nitrosamines (N-nitrosodimethylamine + N-nitrosomorpholine). This threshold is based on the observation of excess mortality from rare cancers, i.e., cancers of the pharynx and the esophagus observed among 8,933 workers employed between 1950 and 1991.

The measured concentrations of nitrosamines in the warehouse of finished rubber products in the Eastern Townships are in the lower limit of the range of concentrations for which carcinogenic effects were statistically associated with increased cancer in a cohort of workers with an average exposure of about 10 years. Despite this and despite the uncertainties associated with epidemiologic studies published in the literature, the existence of mechanisms of action of carcinogens in human tissue cells similar to those observed in rodents incites caution.

In conclusion, since the career of some workers may extends over a period lasting up to 40 years, it seems reasonable that the average exposure limit to NDMA in ambient air be set at lower than 2.5 µg/m^3 in order to protect their health. Thus, we recommend that efforts be made to reduce workers' exposure to daily average concentrations of total nitrosamines below 1 µg/m^3 (8 hours/day, 40 hours per week).

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LIST OF ABBREVIATIONS

ACGIH	American Conference of Industrial Hygienists
CSST	Commission de la santé et de la sécurité du travail
EPA	Environmental Protection Agency
IARC	International Agency for Research on Cancer
INSPQ	Institut national de santé publique du Québec
LOAEL	Lowest-Observed Adverse Effect Level
MBS	Morpholinomercaptobenzothiazole
NDEA	N-nitrosodiethylamine
NDIPA	N-nitrosodiisopropylamine
NDMA	N-nitrosodimethylamine
NEPhA	N-nitrosomethylphenylamine
NIOSH	National Institute for Occupational Safety and Health
NMOR	N-nitrosomorpholine
NOAEL	No Observed Adverse Effect Level
NO_x	Nitrogen Oxides
NPip	N-nitrosopiperidine
NPyr	N-nitrosopyrrolidine
NTP	National Toxicology Program
WHO	World Health Organization
OSHA	Occupational Safety and Health Administration
SIR	Standardized incidence ratio
SMR	Standardized mortality ratio
TMTD	Tetramethylthiurame disulphide
US-EPA	United States Environmental Protection Agency
WHMIS	Workplace Hazardous Materials Information System
ZDEC	Zinc diethyldithiocarbamate

1 INTRODUCTION

1.1 OBJECTIVES

To assess whether workers employed in a warehouse of finished rubber products in the Eastern Townships are at risk of contracting cancer due to the presence of nitrosamines in the air, those molecules being considered carcinogenic by several public health agencies worldwide. And, if the risk is found to exist, suggest a threshold limit not to be exceeded to make the risk negligible.

1.2 NITROSAMINES: DEFINITION

Nitrosamines are molecules consisting essentially of nitrogen and oxygen. They represent a large family of hundreds of molecules whose mixtures vary according to their source. They are formed from amines and nitrosating compounds such as nitrite and NOx, both endogenously (in the body of mammals) and exogenously (environmental). The characteristics of nitrosamines vary from one molecule to another.

1.3 SOURCES OF EXPOSURE TO NITROSAMINES

There are multiple sources of human exposure to nitrosamines including food, tobacco, cosmetics and industrial emissions, mainly from the rubber industry (Tricker, 1997). In fact, nitrosamines that reach the human bloodstream may originate from endogenous sources (synthesized in the stomach from precursors ingested through food) or exogenous sources (absorbed already preformed).

1.3.1 Endogenous sources

Food is the source of endogenous exposure. After absorption of precursors in food (amines and nitrosating agents), nitrosamines are formed by chemical reaction in the acidic gastric juice. The precursors to nitrosamines in the diet are found in foods such as cured nitrites and nitrates used as preservatives, in the amines contained in meat, cheese and vegetables, in meat and fish preserved by smoking (nitrogen oxides found in the smoke can act as nitrosating agents) and foods dried by combustion gas such as malt in beer and whiskey (Liteplo and Meek, 2002).

Owing to measures imposed on food manufacturers in industrialized countries to reduce the use of precursors to nitrosamines, in order to lower the risk of cancer that may be due to those substances, food today has a minor contribution to total exposure of humans to nitrosamines. For example, in 1964, Health Canada banned the use of nitrate for the conservation of seafood, and in 1975, it forced a reduction in the use of nitrites and prohibited the use of nitrates in the treatment of food by salting. (Environment Canada – Health Canada, 2001).

1.3.2 Exogenous sources

Smoking, cosmetics and industrial emissions are the main exogenous sources of exposure. Foods as exogenous source have a minor contribution to total exposure to preformed nitrosamines. The use of nitrite in bacon leads to very low levels of preformed nitrosamines. For normal consumption of bacon, absorbed doses are very low. It was shown that beer, whiskey and other alcoholic beverages brewed from malt contain very low levels of preformed nitrosamines. Over the past decades, by changing preparation processes, manufacturers have greatly reduced these substances in beverages and food.

Smoking is the largest source of non-occupational exposure to nitrosamines. Smokers are heavily exposed to nitrosamines, as large quantities of tobacco-specific nitrosamines are formed by nitrosation of nicotine during the fermentation process (Reichl, 1984). Tobacco-specific nitrosamines are inhaled by the smoker with the primary smoke stream (about 1-4 µg of NDMA per cigarette) and are released at concentrations 20-100 times higher with the gas phase of the current secondary smoke stream. This results in high "passive smokers" exposure to nitrosamines, up to 0.6 µg/h (Reichl, 1984). However, with the presence of filters in cigarettes today, the current exposure may be different from that estimated in 1984.

In occupational settings, the highest concentrations of nitrosamines in the air have been measured in the rubber products industries (Straif et al., 1998, 2000a, 2000b). They are generated during the vulcanization[1] process by nitrosation of accelerators and amine chemical stabilizers by nitrosating agents, or by nitrogen oxides (NO_x) present in the atmosphere of industry, and/or nitrites and nitrate content in salt baths or of unknown sources (Oury et al., 1997; Iavicoli and Carelli, 2006).

Accelerators and chemical stabilizers commonly used as vulcanization agents are tetramethylthiuram disulphide (TMTD), zinc diethyldithiocarbamate (ZDEC) and morpholinomercaptobenzothiazole (MBS). These molecules are the precursors of the main volatile nitrosamines found in the atmosphere of environments where vulcanization is used, from the manufacture to the storage of rubber products. These nitrosamines are N-nitrosodimethylamine (NDMA), N-nitrosodiethylamine (NDEA) and N-nitrosomorpholine (NMOR). However, other nitrosamines may be produced in much smaller quantities in this type of industry, or N-nitrosodiisopropylamine (NDiPA) nitrosodibutylamine (NDPA), N-nitrosopiperidine (NPip), N-nitrosopyrrolidine (NPyr), N-nitrosomethylphenylamine (NEPhA).

In general, in all countries where nitrosamines' sampling was carried out in the rubber industry, NDMA is the nitrosamine which is usually found in greater concentrations (Appendix 1). This was the case in the six plants in the Eastern Townships where air samples were undertaken. There, NDMA accounted for about 80% of total nitrosamines measured.

[1] Vulcanization is commonly used to produce large linear profiles, joints or tubing for the automotive, appliance and construction industries

1.4 N-NITROSODIMETHYLAMINE (NDMA)

The chemical structure of NDMA is illustrated below (Figure 1) and its characteristics are presented in table 1.

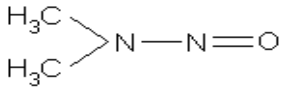

Figure 1 Chemical structure of N-nitrosodimethylamine

NDMA is the simplest dialkylnitrosamine; its molecular formula is $C_2H_6N_2O$ and its molecular weight is 74.08 g/mol (ATSDR, 1989). NDMA is also known under the names of dimethylnitrosamine, dimethylnitrosoamine, N, N-nitrosodimethylamine, N-methyl, N-nitrosodimethylamine, N-nitroso, N-Ndiméthylamine, DMN and DMNA. This is the molecule whose physicochemical properties, pharmacokinetics and toxicity have been studied the most. It is also the most measured nitrosamine in industrial settings and in the general environment.

Table 1 Physico-chemical properties of NDMA

Physicochemical properties	Value
Fusion point	- 50°C
Boiling point	151-154°C
Log K_{oe}	- 0,57
Vapor	1 080 Pa (25°C)
Henry's Law Constant	3,34 Pa·m³/mol (25°C)
Solubility	miscible

CAS Number 62-75-9.

In addition to being highly volatile, this molecule does not bioaccumulate in the environment and biological organisms. Absorption of NDMA is mainly through the respiratory and digestive tracts, sometimes through the dermal tracts (Environment Canada – Health Canada, 2001; Liteplo and Meek, 2002). It was once used in the formulation of flame delaying agents, as additive for industrial lubricant and others, but it no longer has industrial or commercial use in Canada (Environment Canada – Health Canada, 2001).

NDMA is classified as genotoxic carcinogen in animals. Several organizations have classified it in their respective classification grid based on the risk of cancer in humans (Table 2).

Table 2 Classification of NDMA by various legislator organizations or agencies establishing standards

Organization	Classification	
IARC[a]	**2A**	Probably carcinogenic to humans.
CSST	**C2**	Suspected carcinogen in humans.
ACGIH	**A3**	Confirmed carcinogen in animals; transposition in human is unknown.
EPA	**B2**	Reasonably anticipated carcinogen.
OSHA		Potential occupational carcinogen.
WHO	**B2**	Reasonably anticipated carcinogen.
NIOSH		Potential occupational carcinogen.
NTP	**R**	Substance is reasonably anticipated carcinogen.
WHMIS	**D1A**	Very toxic material with immediate and serious effects.
	D2A	Very toxic material causing other toxic effects (carcinogenic, embryotoxic, teratogenic, mutagenic and toxic for reproduction).
	D2B	Toxic material causing other toxic effects (mutagenic to cells not related to reproduction).

[a] IARC has also attributed the notation 2A [Probable human carcinogen] to nitrodiethylamine (NDEA) and 2B to different other nitrosamines.

IARC: International Agency for Research on Cancer.

CSST: Commission de la santé et de la sécurité du travail (Québec's workman compensation board).

ACGIH: American Conference of Industrial Hygienists (USA).

EPA: Environmental Protection Agency (USA).

OSHA: Occupational Safety and Health Administration (USA).

WHO: World Health Organization.

NIOSH: National Institute for Occupational Safety and Health (USA).

NTP: National Toxicology Program (USA).

WHMIS: Workplace Hazardous Materials Information System (Canada).

1.5 WORKPLACE STANDARDS

In Québec, there is no occupational exposure limit (OEL) for nitrosamines, but NDMA is designated by the *Règlement sur la santé et la sécurité du travail* (Québec's health and safety regulations) as a substance to which exposure should be minimized. The situation is similar in the United States and in France, where it is recommended that exposure be reduced to the lowest possible level, but standards exist in some European countries. In the Netherlands, the Dutch Expert Committee (1999) suggests a limit of 0.2 µg/m^3 and Switzerland 1 µg/m^3 for NDMA.

In Germany, the occupational exposure limits vary by industry and are expressed as total nitrosamines. In the chemical industry (polyacrylonitrile fibers), in the tire industry (storage), in the rubber products industry and in the leather industry, the OEL is 1 µg/m³, whereas in the chemical industry (amines) and in the tire industry (vulcanization) it's 0.5 µg/m^3 and it's 0.2 µg/m^3 for cutting fluids, volatile corrosion inhibitors, smelters and other chemical industries other than those listed above (BGIA/GESTIS, 2009)

1.6 CANCER RESEARCH

1.6.1 Experimental studies

Since NDMA is the dominant molecule in the warehouse of finished rubber products in the Eastern Townships, we will limit our analysis to cancer studies conducted in rodents exposed to this molecule orally or via the respiratory tract. Those studies were judged most relevant to explore the risk to workers whose occupational exposure is mainly through inhalation, as well as in non-occupational settings where exposure is by inhalation for smokers and through the diet for non-smokers. Studies in which exposure routes were subcutaneous, intramuscular and intraperitoneal were therefore not analyzed.

Several experimental studies have been performed for chronic exposure to NDMA by different routes of exposure (oral, inhalation, intra-tracheal, subcutaneous, intramuscular and intraperitoneal). In the fifties, Magee and Barnes demonstrated the carcinogenic potential of NDMA in rats by exposing them in their diet at doses of 0.5, 10 and 20 mg/kg bw[2] for 50 days (Magee and Barnes, 1956). They observed a significant increase in liver cancer in groups exposed to 10 mg/kg bw (33%) and to 20 mg/kg bw (83%) compared with controls (0%).

Since then, nitrosamines have been the subjects of extensive studies in laboratory animals. Approximately 90% of the 300 tested nitrosamines have shown carcinogenic effects in bioassays from over 39 animal species (Bogovski and Bogovski, 1981; Rounbehler and Fajen, 1983). The carcinogenic effects of nitrosamines have been observed in several organs, the site of tumour growth depending on the nitrosamine molecule tested, the tested species and the route of administration. The predominant sites of tumors' induction are the liver, the esophagus, the lung, the nasal cavities, the stomach, the kidney, the bladder and the brain. (IARC, 1978; Peto et al., 1991a and b).

In rodents, the genotoxic mechanisms involved in carcinogenesis have been well demonstrated with NDMA. In vitro studies have shown that these mechanisms exist in liver tissues of several animal species (Bartsch et al., 1976) and on cultured human tissue, i.e., liver cells (Montesano and Magee, 1970), colon (Autrup et al., 1977 and 1978), bronchi (Harris et al., 1977) and oesophagus (Harris et al., 1979; Autrup and Stoner, 1982). Moreover, DNA molecules of liver cells from humans intoxicated with NDMA contained the methylated purines N^7-methylguanine and O^6-methylguanine, indicating alterations in DNA by NDMA (Herron and Shank, 1980).

[2] bw: body weight.

In 1999, in response to a request from the Minister of Social Affairs, a Dutch experts committee on workplace standards belonging to the Health Council of the Netherlands[3] performed a study to estimate the additional risk of cancer caused by exposure to NDMA during a career lasting 40 years (Health Council of the Netherlands, 1999).

The committee identified five studies of cancer in rodents (all in rats) exposed orally and four studies in rodents (3 in rats and one in mice) exposed by inhalation and one study in hamsters exposed intratracheally. Tumors were observed in all those studies. However, in most of them, the minimum doses administered were too high (> 1 mg NDMA/kg bw/day) to be considered in our risk analysis, bearing in mind that the exposure of workers in the warehouse of finished rubber products is at most equivalent to a few mg NDMA/kg bw/day.

Note that in studies where at least one exposure dose was less than 1 mg NDMA/kg bw/day, the cancers observed were of the same type as in the studies where all exposure levels were above that value. These are cancers of the liver and the lung for studies where the route of exposure was oral and nasal cavities and cancers of the lung, liver and kidney for exposure by inhalation. Here is the list of studies that will be discussed in the section "Analysis of experimental studies" of this report.

Oral exposure

1. Peto et al., (1991a and b). Groups of 60 male and female Colworth rats were exposed throughout their lives to 15 different doses of NDMA and NDEA. The number of tumors observed was compared to that observed in a control group.

NOTE: These two articles are based on the same experiment. The difference between the two is the duration of experience follow-up and the type of data analysis.

Inhalation exposure

1. Moiseev and Benemanskiï (1975a). Study on male and female Wistar rats exposed to NDMA compared to unexposed group.
2. Moiseev and Benemanskiï (1975b). Study on male and female mice exposed to NDMA compared to unexposed group.
3. Klein et al., (1991). Four groups of Sprague-Dawley rats exposed to NDMA.

1.6.2 Historical analysis of cancer risks for workers in the rubber industry worldwide

Before 1978, no epidemiological study has been published on the cancer risks for workers in the rubber industry. Then, in 1978, the International Agency for research on Cancer (IARC) published a monograph on the carcinogenic risk of chemicals to humans. In that report, the authors indicated that, although no epidemiological study was available (and efforts should be headed in that direction), NDMA should be considered carcinogenic to humans (IARC, 1978).

[3] Dutch Expert Committee on Occupational Standards, a committee of Health Council of the Netherlands.

This conclusion was thus established:

1. based on animal studies that showed clearly, in several animal species, the link between exposure to NDMA and increased incidence of several types of cancers, and
2. based on the observation of similarities between the metabolism of nitrosamines found in rodent tissues and that found in human cells.

They then ranked the N-nitrosodimethylamine in Group 2A (probably carcinogenic to humans) and considered that previously, the most exposed workers were in the rocket fuel industry and the pesticide industry.

In 1982, an IARC working group published an evaluation of carcinogenic risks in the rubber industry, i.e., the risks associated with all carcinogens in this industry and not only with nitrosamines (IARC, 1982). That evaluation included a few epidemiological studies (cohort and case-control) undertaken in this industry in Great Britain, the US, Switzerland and Finland. In all, 33 epidemiological studies are cited in the IARC report of 1982. The British cohort included workers who were employed in this industry since 1911, since 1940 in the American study, since 1955 in the Swiss study and since 1953 in the Finnish study. At that time, the IARC working group considered that there was sufficient evidence to conclude that working in this industry could be associated with an increased cancer risk to workers. An association of cause and effect was attributed to leukemia and cancer of the bladder. For cancers of the lung and stomach the authors could not exclude the possibility that factors other than those related to occupation could be the cause. The strength of the evidence was considered insufficient for cancers of the skin, prostate, colon and lymphomas, and inadequate for cancers of the brain, thyroid and pancreas.

However, the report's authors cite several limitations to the studies examined such as, the lack of exposure assessment, the inability to estimate the exposure that occurred over the past decades, the presence of frequent inconsistencies between jobs held by workers and their actual exposure to agents of interest and the lack of control of confounding factors such as smoking and diet.

They added that it was likely that the cause of cancers observed in the rubber industry is more attributable to an exposure to a combination of chemicals in that industry rather than to a single substance or a particular family of substances. According to them, the variety of exposure to various risk factors in professional and non-professional environments increases the likelihood of effects due to the interaction of these factors. They note that experimental studies have shown the mutagenic and carcinogenic potential of several products present in the atmosphere of rubber products plants. They list the following products: mineral oils, extracts of carbon black, vulcanization smoke, nitroso compounds and aromatic amines, some monomers, solvents, nitrosamines, thiuram and dithiocarbamate compounds, the ethylenethiourea, di(2-ethylhexyl) phthalate, di(2-ethylhexyl) adipate and hydrogen peroxide.

The authors provide some explanations for their decision to assign a causal link between the increased incidence of certain cancers and working in the rubber industry.

- An excess mortality from bladder cancer is clearly demonstrated in workers who have worked in the rubber industry in England before 1950, especially in jobs with high probability of exposure to aromatic amines. Since the discontinuation in 1949 of certain antioxidants containing 2-naphthylamine used in this industry, a substantial decline in bladder cancer was observed.
- They do not exclude that improvement in industrial hygiene practices and awareness of cancer risks in this industry may have contributed to such decline.
- They believe that the excess of mortality from leukemia could be attributed to the presence in these workplaces of solvents such as benzene.
- They stated that lung cancer was positively related to a variety of jobs. However, it could not be attributed to specific factors found in the workplace.
- They consider that cancer of the stomach, which is high in the UK and U.S. industries, appears to be associated with jobs at the start of production lines including preparation, mixing, molding and extrusion.

In 1987, the IARC published an updated assessment of the risk of cancer in the rubber industry carried out in 1982 (IARC, 1987). The Working Group maintains the levels of evidence established in 1982 on the excess of specific cancers and causal association with occupational exposure.

Following the publication of the IARC in 1982, many epidemiological studies on cancer risk for workers in the rubber industry worldwide have been published. Kogevinas et al. (1998) undertook a review of epidemiological studies published between 1983 and 1997. They identified 12 cohort studies from nine countries, seven case-control studies within a cohort, 48 case-control studies in the general population and 23 studies based on administrative data in 16 countries (Kogevinas et al., 1998). Their analysis focused on the incidence of cancer and on the mortality rate due to all causes including cancer, all causes of cancer and various types of specific cancers. They analyzed these rates separately for cohort studies and for case-control and administrative studies. It is worth mentioning that their analysis was not a meta-analysis itself. In other words, they did not follow a statistical approach combining results from a series of independent studies on a particular problem for more precision in the results.

They presented the range of relative risks (RR), odds ratios (OR), standardized incidence ratios (SIR) and standardized mortality ratios (SMR) observed in the study groups analyzed, i.e. average minimum and maximum values, without specifying the confidence interval due to these values. Moreover, for the cohort studies and the case-control studies, they reported separately the number of studies showing excess risk and those for which there was no excess risk. The authors justified their approach by citing the heterogeneity of exposure within a single plant and between plants, the differences between studies in the classification of occupational exposures (types of employment, types of industry, tasks, number of years of

employment, etc.) and the differences in the study design which did not allow to place great value on the calculation of an overall risk incorporating all studies.

Note that some cohort and case-control studies cited in this review are the updates of studies published before 1982. These had been considered in the IARC evaluation in 1982. We present below the findings of Kogevinas et al. (1998) assessment.

- The analysis of epidemiological studies shows that the risk is highest among workers employed before 1960 than after that date.
- A moderate excess of mortality from bladder cancer, lung cancer and leukemia is observed in a majority of studies, and this, in different regions of the world.
- A slight excess of mortality from larynx cancer is observed. The authors state that the number of cases in each study was low and that no study showed a statistically significant excess of mortality from this type of cancer.
- There is an indication of a possible excess of mortality from lymphoma, pancreatic cancer and brain cancer, but there is inconsistency between studies. There is little evidence of an excess mortality from cancer of the stomach.
- The data on exposure levels in the workplace are absent in almost all published studies.

Thus, the authors conclude that on the basis of these studies, an estimated cancer risk due to specific substances or to a specific process in the rubber industry is not possible.

In 1998, IARC published an updated assessment of the risk of cancer in the rubber industry carried out in 1982 and in the preceding update in 1987 (IARC, 1998). The IARC conclusions on the evidence of cancer risk in this industry had changed very little since 1982. Since this is the last update of the IARC, we present in table 3 the conclusions regarding the levels of evidence of excess cancers and causation.

Table 3 Assessment of the risk of cancer in the rubber industry by the IARC – Last Updated (IARC, 1998)

Level of evidence[a]	Type of cancer[a]	Suspected causative agent or category of use
Sufficient for the excess incidence among workers and a causal association with occupational exposures	Bladder Leukemia	Aromatic amines Solvents
Sufficient for the excess incidence among workers and ***limited*** for a causal association with occupational exposures	Stomach Lungs	Preparation, mixing and molding Varied
Limited for the excess incidence among workers and a causal association with occupational exposures	Skin	Tire Plant
Limited for the excess incidence among workers and ***inadequate*** for a causal association with occupational exposures	Colon Prostate Lymphoma	
Inadequate for the excess incidence among workers and a causal association with occupational exposures	Brain Thyroid Pancreas Esophagus	

[a] The Working Group stated that this list does not imply that the risk of cancer is universal in all rubber product plants in all countries or that the estimated level of evidence applies to all situations.

In general, until 1998, the published epidemiological studies sought to verify the link between excess of mortality from specific cancers or cancer mortality and type of industry (tires, various rubber products), the tasks, the year hired, the duration of employment in the factory or at a particular task. However, exposure to various carcinogenic contaminants contained in the rubber was not evaluated (nitrosamines) no more than confounding factors such as smoking (exception: Zhang et al., 1989), the socio-economic level and other potentially carcinogenic contaminants found in the ambient air of the rubber industry (solvents, asbestos, talc, aromatic amines, etc.). Note that in the study by Zhang et al. (1989), controlling for smoking had led to reduce the risk of lung cancer observed before this control, but not eliminate it completely.

Thus, on the basis of these data it would be impossible to establish a relationship between exposure to nitrosamines and the risk of cancer. However, knowledge of this relationship is essential to achieving our goal which is to try to estimate the cancer risk incurred by employees working in a warehouse of finished rubber products in the Eastern Townships due to the presence of nitrosamines in their work environment.

Fortunately, after 1998, German researchers have conducted a series of epidemiological studies in order to better comprehend the risk factors for cancer in the rubber industry in Germany (Weiland et al., 1996 and 1998; Straif et al., 1998, 2000a and 2000b).

These five studies have examined the same cohort that included more than 11,000 employees working in five factories producing tires and other rubber products. That cohort had been created at the beginning of the decade in order to initiate a comprehensive epidemiological investigation to better understand the health risks of workers working in the German rubber industry. It was presented in 1996 in the first article related to this investigation in which Weiland et al. (1996) explained the methodology used to conduct this investigation. The authors also presented the results of an initial assessment of risk of death from cancer in the German industry in connection with time-related factors: year hired, year of employment termination and number of years between the death of the subjects and the termination of employment. The authors' observations prompted them to continue the analysis of this cohort in order to ascertain whether the observed excess risk of mortality from certain cancers was related to work areas, types of employment or presence of specific contaminants in such workplaces. Note that the epidemiological study of Weiland et al. (1996) was part of the epidemiological review conducted by Kogevinas et al. (1998) and of the update of the IARC in 1998, for which we presented the findings above.

In pursuit of this large epidemiological investigation initiated by Weiland et al. (1996), four subsequent epidemiological studies have been published: those of Weiland et al. (1998), Straif et al. (1998) and Straif et al. (2000a and b). The authors of these studies have examined risk of death from specific cancers among workers in German factories in relation to the various categories of tasks or work areas and in relation to exposure to nitrosamines (NDMA and NMOR) and other potentially carcinogenic contaminants (asbestos, talc, carbon black and dust) present in the workplace at these plants. One of these categories applies to workers in the storage and dispatch areas of rubber products factories, i.e., the type of employment covered by this study.

For these reasons, these four studies (Weiland et al., 1998; Straif et al., 1998, 2000a and 2000b) will be discussed in detail in the pursuit of our objectives. The study by Weiland et al. (1996) will also be analyzed since it allows to present the original cohort of the large epidemiological investigation and to put into context the other four subsequent studies.

2 METHODOLOGY

The approach used for the risk analysis concerning workers in a warehouse of finished rubber products in the Eastern Townships has three components.

Component 1: Estimating the exposure to nitrosamines of those workers and comparing it to that of workers elsewhere in the world.

The workers' daily average exposure and cumulative dose will be estimated based on concentrations of nitrosamine (NDMA and total nitrosamines) measured by the occupational health teams in ambient air of the warehouse in the Eastern Townships.

The range of average daily exposure will then be expressed in µg/kg of body weight (bw) by considering the range of concentrations (expressed in µg of NDMA/m^3 and µg of total nitrosamines/m^3 of air) and assuming that a working adult weighs between 70 to 90 kg and inhales about 10 m^3 of air per day.

The cumulative dose for workers will be estimated in µg of nitrosamines/kg bw/year by multiplying the daily dose by 5 days/week x 50 weeks/year x number of years of work.

Finally, workers exposure to nitrosamines in the warehouse of finished rubber products in the Eastern Townships will be compared with those of workers in the rubber industry around the world for which there is data in the literature and with the non-occupational exposure to nitrosamines in Canada.

Component 2: Evaluation of the carcinogenicity of NDMA in humans and if possible, determining the "dose-response" relationship or a threshold without effect.

We believe that there is sufficient evidence of a carcinogenic effect of nitrosamines in animals. In addition, metabolites of nitrosamines considered mutagenic in animals were also present in the tissues of humans exposed to these molecules. Thus, in the present risk assessment of cancer in humans, these observations will be considered and analyzed in detail in order to verify whether the results of animal studies may be applied to humans. This assessment will include the following:

1. An analysis of cancer studies in animals and analysis of the "*dose - cancer excess*" relationship observed following oral or pulmonary exposure to NDMA.
2. Analysis of the influence of the differences in pharmacokinetics (absorption, distribution and elimination) and pharmacodynamics (mechanisms of action) of NDMA and its metabolites between species on the risk of cancer.
3. Analysis of the epidemiological studies carried out by researchers in Germany for the reasons that we just described (Weiland et al., 1996, 1998; Straif et al., 1998, 2000a and 2000b).
4. Analysis of a British epidemiological study focusing on employees in the rubber industry hired after 1982 (Dost et al., 2007).

Component 3: Estimating cancer risk for workers in the industry.

This risk assessment will be conducted by comparing workers' exposure to nitrosamines (component 1) to results obtained in the analysis of carcinogenicity (component 2). We will try to answer frequently asked questions raised by cancer risk analysis related to chemicals.

1. Can we reject the hypothesis of a causal link between exposure to nitrosamines and cancer induction in humans?
2. If such a relationship was not rejected, what is the best determinant of cancer risk associated with nitrosamines? The cumulative dose? The frequency of exceeding a certain concentration?
3. Is there a threshold below which cancer risk linked to chronic exposure would be nil or negligible, at least undetectable with the means at our disposal?

3 RESULTS

3.1 EXPOSURE TO NDMA

3.1.1 Occupational exposure to nitrosamines identified in the literature

Unlike epidemiological and animal studies linked to nitrosamines, there are few published data on occupational exposure to nitrosamines in the manufacturing of rubber products. Indeed, for the period 1983-2009, only seven articles were found in the literature on sampling of nitrosamines in the workplace in various countries. A brief description of these articles is presented in Appendix 1.

Several nitrosamines have been sampled in these studies (NDBA, NDEA, NDMA, NMOR, NPIP, NPYR and total nitrosamines), and measured concentrations generally range from one hundredth to one tenth (0.01 to 0.1) of µg/m³. However, NDMA, NMOR and total nitrosamines are often found at higher levels, up to several µg/m³.

Analysis of these data shows that, overall, the levels of NDMA and total nitrosamines in the work environment of plants around the world are comparable if not higher than those found in the factory and the warehouse of rubber products in the Eastern Townships. Note that some of these studies are several years old and that the measurements were generally conducted to quantify and subsequently reduce exposure to nitrosamines generated by various processes.

The samples were collected during the manufacturing of various rubber products (sealing strips for the automotive industry, drive belts, tires, hoses, gaskets, etc.). However, there was little data on workers' exposure in warehouses. Only one article published in 1983, reported levels of NDMA measured in the storage and dispatch areas of tires and inner tubes, ranging from 0.2 to 19 µg/m³ (Spiegelhalder and Preussmann, 1983).

Furthermore, there were no articles linking the exposure levels found in the rubber industry and the effects on health. However, some epidemiological studies examined some health effects observed with reference to the duration of exposure, time elapsed since the first contact or categories of estimated exposure based on expert opinion or based on the history of exposure in each type of industry.

3.1.2 Estimated workers' exposure to nitrosamines in the warehouse of finished rubber products in the Eastern Townships

Concentrations of NDMA and total nitrosamines in the warehouse

Between 2005 and 2008, the occupational health team of the CSSS du Haut-St-François has undertaken several samplings of total nitrosamines and NDMA at various sites in the warehouse of finished rubber products. After consulting with the CSSS team, and for purposes of estimating workers' cumulative exposure, it was decided to retain only representative samples of a plausible occupational exposure.

Thus, 15 individual samples (general work and forklift operator), 19 ambient samples (various locations in the warehouse, near or inside shipping trailers) and five ambient samples (offices) were selected for this report. Two samples carried out in outdoor air, in 2005 and 2006, showed levels below the detection limit (< 0.06 µg/m³) for both NDMA and total nitrosamines. They are mentioned here for informational purposes.

The comparison of the 34 sampling results undertaken in the warehouse revealed no statistically significant differences between the individual and the ambient sampling results ($p > 0.01$, Mann-Whitney). Consequently, it was possible to pool them to assign a cumulative exposure to NDMA and total nitrosamines to the entire warehouse. On the other hand, comparing these 34 results with those obtained from sampling in the offices ($n = 5$) showed a statistically significant difference: it was therefore decided to treat the 5 samples separately. However, since the statistical analysis is based on a small number of results, data interpretation must be done with caution.

Regarding NDMA, the results ranged from 0.41 to 9.90 µg/m³, with arithmetic means between 0.93 and 3.75 µg/m³ depending on the selected task or site. These levels fall within the range of the results reported by Spiegelhalder and Preussmann (1983), in the storage and dispatch areas of tires and inner tubes, in Germany (0.2 to 19 µg/m³). Half of the 34 results were below 2.5 µg/m³, with an overall arithmetic mean of 3.1 µg/m³ (Table 4).

Table 4 Results of NDMA sampling in the warehouse of finished rubber products in the Eastern Townships

Task or site	Number of results	Sampling	Arithmetic mean (µg/m³)	Geometric mean (µg/m³)	Median (µg/m³)	Range
General worker	7	Individual	2.57	2.31	2.60	0.70-4.20
Forklift operator	8	Individual	2.12	1.97	2.30	0.63-2.60
Various locations in the warehouse	19	Ambient	3.75	3.16	2.80	0.70-9.90
Total of the three categories	**34**		**3.13**	**2.65**	**2.50**	**0.63-9.90**
Offices	5	Ambient	0.93	0.80	0.67	0.41-1.60

With respect to total nitrosamines, the results ranged from 0.46 to 11.43 µg/m³, with arithmetic means of 1.19 to 4.59 µg/m³ depending on the selected task or site. Half of the 34 combined results are below 3.5 µg/m³, with an overall arithmetic mean of 4.0 µg/m³ (Table 5).

Table 5 Results of total nitrosamine sampling in the warehouse of finished rubber products in the Eastern Townships

Task or site	Number of results	Sampling	Arithmetic mean (µg/m³)	Geometric mean (µg/m³)	Median (µg/m³)	Range
General worker	7	Individual	3.43	3.06	3.85	0.88-4.83
Forklift operator	8	Individual	2.89	2.59	2.82	0.74-4.63
Various locations in the warehouse	19	Ambient	4.59	3.96	3.66	1.08-11.43
Total of the three categories	**34**		**3.95**	**3.40**	**3.53**	**0.74-11.43**
Office	5	Ambient	1.19	0.98	1.08	0.46-2.25

Note that NDMA represents nearly 80% of total nitrosamines measured in the warehouse of finished rubber products in the Eastern Townships, which would explain the relatively comparable levels observed in Tables 4 and 5.

Estimating the workers cumulative exposure dose

Based on the data in Tables 4 and 5, we can estimate the cumulative exposure doses of NDMA and total nitrosamines to which the workers in the warehouse are likely to be exposed to during their career. The results of these estimates are presented in table 6. The cumulative exposure dose is expressed in µg/kg of body weight (bw) and is calculated using the following formula:

(Concentration (in µg/m^3) X 10* m^3/day x 5 days x 50 weeks x number of years of work)/80 kg.

* Average volume of air inhaled daily (expressed in m^3) by an adult weighing between 70 and 90 kg.

Thus, excluding office workers, daily exposure doses to NDMA for workers in the warehouse of finished rubber products in the Eastern Townships range from 0.27 to 0.47 µg/kg bw and from 0.36 to 0.57 µg/kg bw for total nitrosamines (Table 6).

Table 6 Cumulative exposure doses of NDMA and total nitrosamines for workers in the warehouse of finished rubber products in the Eastern Townships

Task or site	N	AM[a] (µg/m³)	Per day (µg/kg bw)	Per year (µg/kg bw)	For 10 years (µg/kg bw)	For 45 years (µg/kg bw)
NDMA						
General worker	7	2.57	0.32	80.31	803.10	3613.95
Forklift operator	8	2.12	0.27	66.25	662.50	2981.25
Various locations in the warehouse	19	3.75	0.47	117.19	1171.90	5273.55
Total of the three categories	**34**	**3.13**	**0.39**	**97.81**	**978.10**	**4401.45**
Office	5	0.93	0.12	29.06	290.60	1307.70
Total nitrosamines						
General worker	7	3.43	0.43	107.19	1071.90	4823.55
Forklift operator	8	2.89	0.36	90.31	903.10	4063.95
Various locations in the warehouse	19	4.59	0.57	143.44	1434.40	6454.80
Total of the three categories	**34**	**3.95**	**0.49**	**123.44**	**1234.40**	**5554.80**
Office	5	1.19	0.15	37.19	371.90	1673.55

[a] Arithmetic mean of the measures taken at stationary or personal sites.

3.1.3 Non-occupational exposure to NDMA in Canada

In September 2001, Health Canada and Environment Canada jointly published under the amended Canadian Environmental Protection Act and within the framework of the priority substances list, an assessment report on N-nitrosodimethylamine (NDMA), the nitrosamine generally found in larger amounts as a contaminant in the environment (Environment Canada – Health Canada, 2001).

They reported low levels of NDMA in air, water and soil, except in the vicinity of industrial facilities producing pesticides, automobile tires and alkylamine. They estimated that in Canada, the average daily exposure to NDMA for an adult is about 0.01 µg/kg bw through food and water consumption, excluding the contribution of beer consumption and cigarette smoke (Environment Canada – Health Canada, 2001). They note however that exposure to NDMA in the air of a smoker's environment is estimated to be 0.05 µg/kg bw/day and that an adult smoker consuming 20 cigarettes per day would be exposed to a dose of up to 0.08 µg/kg bw/day (Environment Canada – Health Canada, 2001).

These non-occupational exposure levels of NDMA are well below those estimated for the clerical and warehouse workers of our study ranging from 0.12 to 0.47 µg/kg bw/day (Table 6).

3.2 ANALYSIS OF THE CARCINOGENICITY OF NDMA

3.2.1 Analysis of experimental studies

Studies of cancers in animals chronically orally exposed

Peto et al. 1991a and b

Groups of 60 male and female Colworth rats were exposed for their entire life (average median survival of approximately 2.5 years) to 15 doses of NDMA ranging from 1 to 653 µg/kg bw (administered in water at concentrations ranging between 0.033 to 16.896 ppm NDMA or NDEA). The number of tumors observed was compared to that observed in the control group of 120 male and female rats. These studies included a total of 4,080 rats. Both are based on the same experiment. The difference between the two is the experience follow-up duration and the results analysis' design.

The authors studied separately the risk of an excess mortality from cancer associated with exposure to NDMA or NDEA. They also studied the survival of animals depending on the exposure dose. In our opinion, this experimental study is of high quality methodologically, and in regards to its completion and data analysis. It involves multiple doses, several animals per dose, all cancer types have been analyzed taking care to reflect rates of cancers observed and expected in the exposed group. The follow-up of rats was performed until natural death occurred, i.e., in some cases over a period of more than 3.5 years. Note that in experimental cancer studies, rats are generally sacrificed after 2 years of life. This results in not being able to observe the natural increased rate of death from cancer in the last months of life. Yet, like the age dependent cancers seen in humans, this rate increases very rapidly in animals at the end of their life.

Results

The authors recorded an association between the increased incidence of benign and malignant tumors of the liver and associated organs (bile duct and gallbladder) and the increasing doses of NDMA and NDEA. In addition, the NDEA was also associated with an increased incidence of tumors of the esophagus, while NDMA did not affect this organ. Tests for trend between dose and number of animals affected by various types of lesions, affecting other organs or tissues (benign and malignant) suggest a link between increasing the dose of NDMA and increasing the incidence of tumors affecting the lungs, the skin and the lymphatic and hematopoietic tissues. Unlike tumors of the liver, in the case of those tissues and organs, the authors did not exclude the effect of chance for these observations, because of the weak relationship observed.

Since our study focuses on NDMA for the reasons mentioned in the introduction, we only analyze the data related to this molecule. We present in table 7, the results of the observations of Peto et al. (1991a) in connection with liver cancer.

Table 7 Dose-response relationship for fatal liver neoplasms in male and female rats – control groups and groups exposed to NDMA (Peto et al., 1991a)

Treatment group	NDMA (ppm)	Male			Female		
		Dose (µg/day/kg)	Death observed (O)	Ratio (O/E[a])	Dose (µg/day/kg)	Death observed (O)	Ratio (O/E)
1	0	0	1	0.01	0	1	0.01
2	0.033	1	1	0.04	2	1	0.03
3	0.066	3	3	0.13	5	0	0.00
4	0.132	5	3	0.14	10	2	0.07
5	0.264	11	3	0.14	19	3	0.10
6	0.528	22	3	0.13	38	5	0.17
7	1.056	44	5	0.24	96	5	0.16
8	**1.584**	67	3	0.14	**115**	**27**	**1.10**
9	**2.112**	87	13	0.60	**153**	**33**	**1.30**
10	**2.640**	**109**	**27**	**1.60**	**191**	**44**	**2.10**
11	**3.168**	**131**	**33**	**1.90**	**229**	**48**	**2.50**
12	**4.224**	**174**	**36**	**2.50**	**306**	**53**	**3.30**
13	**5.280**	**218**	**46**	**4.40**	**382**	**52**	**4.60**
14	**6.336**	**261**	**49**	**5.20**	**459**	**51**	**4.90**
15	**8.448**	**348**	**55**	**8.60**	**612**	**55**	**10.00**
16	**16.896**	**697**	**59**	**34.50**	**1224**	**58**	**30.80**
Total			340	1.00		438	1.00

[a] Death rates from liver neoplasms observed in those exposed compared to that expected in the unexposed.

The analysis of the data in table 7 indicates that there is an increased risk of liver cancer (observed/expected > 1) from the daily dose of 109 µg NDMA/kg bw in male rats and from 115 µg NDMA/kg bw in female rats.

In table 8 we calculate the cumulative dose during periods of one year and 2.5 years of exposure to doses corresponding to the lowest-observed adverse effect level (LOAEL) and the no observed adverse effect level (NOAEL) observed in these animals for liver cancer. Note that depending on the dose, the rats' survival rate ranged from 1 year (rat group No. 10) to 2.5 years (rat group No. 7): the survival rate decreases as the dose increases.

Table 8 Cumulative dose of oral exposure in male and females rats calculated on the basis of exposure to NDMA of rat groups 7-10 in Peto's studies (1991a and b)

Groups of rats exposed to critical doses	Concentration (ppm)	Per day (µg/kg bw)		Per year (µg/kg pc)		For 2.5-year (µg/kg pc)	
		male	female	male	female	male	female
7	1.056	44	96	9108.0	19872.0	22770.0	49680.0
8	1.584	67	**115**	13869.0	23805.0	34672.5	59512.5
9	2.112	87	153	18009.0	31671.0	45022.5	79177.5
10	2.640	**109**	191	22563.0	39537.0	56407.5	98842.5

By comparing the cumulative doses for workers in the warehouse of finished rubber products in the Eastern Townships in table 6 with those in table 8, we note that the daily and annual doses for workers are about 100 times lower than those of rats for which there is an excess mortality from liver cancer in Peto's studies (1991a and b).

The studies of Peto (1991a and b) served as a basis for several organizations to estimate the cancer risk in humans by extrapolating, with mathematical modeling, the data for liver cancer observed in Colworth rats. Generally, with these approaches, the estimated daily doses to induce an excess risk of mortality from cancer in humans of about 1 per 100,000 and 1 per 1 million are very low (EPA 1987; Health Council of the Netherlands, 1999; Fitzgerald, 2007). For example, for NDMA, EPA-USA estimates that the dose is 7×10^{-4} µg/m^3 for an excess risk of mortality from cancer of 1 per 100,000, and 7×10^{-5} µg/m^3 for an excess risk of mortality from cancer of 1 per 1 million (EPA, 1988).

Colworth rats are very sensitive to liver cancer. Indeed, the rate of cancer in the control group in the study of Peto (1991) is about 30%. In North America, the respective rates of primary liver cancer (hepatocellular carcinoma)[4] in men and in women are respectively 5.3 and 1.9/100,000 (Lambert, 2009). This raises the question of the use of those rats as model regarding the risk of human liver cancer.

[4] The main cause of hepatocellular carcinoma in humans is chronic infection by hepatitis B virus (HBV) and C (HCV). Approximately 350 million people are infected with HBV and 170 million with HCV, worldwide. The hepatocellular carcinomas attributable to HBV are common in Asia, Greece and in all African countries except Egypt. Cases attributable to HCV are common in Japan, Egypt, Italy and Spain. Other important causes of hepatocellular carcinoma are the excessive consumption of alcohol in developed countries and aflatoxin in tropical countries.

Studies of cancer in animals chronically exposed by inhalation

Moiseev and Benemanskiï, 1975 (a and b)

1. Moiseev and Benemanskiï 1975a

This study was carried out on male and female Wistar rats. A group of 87 rats exposed for 25 months to a dose of 50 µg NDMA/kg bw/day and a group of 61 rats exposed to a dose of 200 µg NDMA/kg bw/day were compared with a group of 77 unexposed rats.

Results

- Dose of 50 µg NDMA/kg bw/day: no excess mortalities from cancers were observed compared to the control group.
- Dose of 200 µg NDMA/kg bw/day:
  - Lung cancer: exposed group (12/61) and control group (5/77)
  - Liver cancer: exposed group (12/61) and control group (3/77)
  - Kidney cancer: exposed group (32/61) and control group (2/77)

2. Moiseev and Benemanskiï, 1975b

This study was conducted with male and female mice. A group of 77 mice exposed for 17 months at a dose of 50 µg NDMA/kg bw/day and a group of 101 mice exposed to a dose of 200 µg NDMA/kg bw/day were compared with a group of 81 unexposed mice.

Results

- Dose of 50 µg NDMA/kg bw/day: no excess mortalities from cancers were observed compared to the control group.
- Dose 200 µg NDMA/kg bw/day:
  - Lung cancer: exposed group (19/101) and control group (3/81)
  - Liver cancer: exposed group (6/101) and control group (0/81)
  - Kidney cancer: exposed group (4/101) and control group (0/81)

The study of Klein et al. (1991)

Klein et al. exposed four groups of 36 male Sprague-Dawley rats four times a week, to concentrations of 0, 120, 600 and 3,000 µg/m^3 of NDMA, 4-5 h/day for 207 days from the 8th week after birth. The average daily exposure doses were estimated at 0, 10, 45 and 180 µg/kg bw/day, respectively. At the macroscopic observation or palpation of tumors, the rats were sacrificed; otherwise they let them live until death ensues before performing a necropsy. The authors indicate that the nasal tumors were the main tumors observed. They analyzed these tumors in detail histopathologically and at the time of clinical onset. However, they make no mention of other types of tumors that would have been observed in this study.

Table 9 Histopathological findings in rats after chronic inhalation exposure to NDMA: nasal tumors (adapted from Klein et al., 1991)

Comments	NDMA Treatment			
	0 ppm[a] (0 µg/m³)[b] (0 µg/kg/d)[c]	0.04 ppm (120 µg/m³) (10 µg/kg/d)	0.2 ppm (600 µg/m³) (45 µg/kg/d)	1.0 ppm (3,000 µg/m³) (180 µg/kg/d)
Nb rats carrying at least one tumor (benign or malignant)	**0/36 (0%)**	**13/36 (36%)**	**31/36 (86%)**	**19/36 (53%)**
Esthioneuroblastoma		**2** (671)[d]	**2** (562)	**9** (320)
Mucoepidermoid tumor (Benign)		**11** (770)	**30** (662)	**7** (491)
(Malignant carcinoma)			**2** (498)	3 (498)
Squamous cell carcinoma				1 (398)
Neurogenic sarcoma				1 (454)
Osteogenic sarcoma				2 (510)
Cumulative doses over 207 days exposure (mg/kg)	0	2	7,8 - 8,0	20 - 37

[a] Concentration of NDMA in the air expressed in parts per million.

[b] NDMA concentration in the air expressed as µg NDMA/m^3 of inhaled air.

[c] Average daily dose expressed in µg NDMA/kg of body weight/day.

[d] Values in parentheses correspond to the median (in days) of the age of the rats at the onset of tumors.

Table 9 shows that after the first dose of exposure to NDMA (10 µg/kg/d), 13 out of 36 exposed rats were tumor-bearing, compared to 0 case in the controls. Among the 13 rats affected, 11 had benign tumors, two rats were bearing of a mucoepidermoid tissue carcinoma and two had an esthioneuroblastoma (cancer). Note that some rats were bearing more than one tumor.

Unfortunately, unlike the study of Peto et al. (1991a) in which rats were exposed to oral doses up to a minimum of 1 µg/kg/d, in the Klein et al. study, we cannot comment on the "doses administered by inhalation-excess cancers" relationship at doses below 10 µg/kg/day. However, judging by the response at that dose (13 rats with tumors out of 36 exposed), the probability of an excess with doses lower than 10 µg/kg/day is very high.

The incidence of tumor-bearing rats significantly increases with the average dose 40 µg/kg/day (31/36) and decreases with the dose of 180 µg/kg/day (19/36). This decrease is explained by the fact that the survival of the latter group was reduced by nine months compared to the survival of the control group, suggesting the occurrence of deaths due to poisoning at the highest dose before the induction of new tumors. Note that the survival rate of the group of rats exposed to the average dose of 10 µg/kg/day was superior to the control group by two months.

There is a dichotomy between the observations of Moiseev and Benemanskiï (1975a and b) and those of Klein et al. (1991). Indeed, Moiseev and Benemanskiï found no mortality increase from cancer at the dose of 50 µg/kg/d, whereas even at a dose of 10 µg/kg/day,

Klein et al. observed a significant mortality increase from cancers of the nasal passages. Moiseev and Benemanskiï exposed Winstar rats while Klein et al. used Sprague-Dawley rats. That observation leads us to raise the hypothesis that the nasal tissues in Sprague-Dawley rats are more hypersensitive to the NDMA than in Winstar rats. In fact, Hadley et al. (1983) showed that the capacity for biotransformation of toxic substances in the nasal mucosa varies significantly from one species to another.

Another factor that could explain, at least in part, the differences between these studies is the age of the animals at the onset of cancer. In the studies of Moiseev and Benemanskiï, the rats were sacrificed at the age of 2 years while in the study of Klein et al., they let them live until death. Obviously, some cancers appear after the age of 2 years even if the exposure had ceased. However, this does not explain everything because at the dose of 40 µg/kg/d the first cancers occurred before age 2 years, between the 498th and 662nd day, depending on the type of cancer (Table 9).

Jeffrey et al. (2006) indicate that, in studies where biotransformation in rodents and humans is compared, it is generally much higher in rodents. In addition, enzymes and co-enzymes (e.g., the cytochrome P450 types) involved are often different. Cancers of the nasal cavities are rare in humans. According to Bhattacharyya (2002), tumors of the nasal cavity and paranasal sinuses account for less than 0.5% of all invasive cancers in humans, the most frequent being papillomas and squamous cell cancers. Note that no epidemiological study mentions an increase in nasal cancer in the rubber industry.

3.2.2 Analysis of the influence of the different inter-species pharmacokinetics and pharmacodynamics of NDMA on cancer risk

Analysis of the pharmacokinetics

Absorption of NDMA

1. Oral absorption

The kinetics of NDMA has been studied in rats, pigs and dogs (beagle race). In table 10, we summarize the main findings in relation to the kinetics of NDMA in these species.

Table 10 Comparison of the pharmacokinetics of NDMA in rats, pigs and dogs

Species	Doses	Absorption Oral	Clearance (ml/min/kg)	Elimination (Half-life)
Rat[a]	0.15 – 0.3 mg/kg	8%	39.0	10 min
Pork[b]	1.0 – 5.0 mg/kg	67%	65.8	28 min
Dog[b]	1.0 – 5.0 mg/kg	93%	43.3	73 min

[a] Mico B.A et al., 1985.

[b] Gombar CT et al., 1987, 1988.

It appears that the bioavailability rate of NDMA by oral route varies significantly between species. According to Gombar et al. (1988), it increases in most evolved mammals, suggesting that in humans, it would be higher than in pigs and dogs.

This observation has great importance in risk analysis when comparing the results of cancer studies conducted in various animal species with the results of epidemiological studies. For example, if the cumulative absorbed dose required to induce an equivalent percentage of liver cancer in rats was identical to that in dogs, this would mean that rats should be exposed to a dose 11.6 (93%/8%) times higher than that of dogs to reach this level of risk.

2. Absorption by inhalation

Klein and Schmezer (1984) studied the degree of absorption by inhalation of four molecules of nitrosamines, N-nitrosodimethylamine (NDMA), N-nitrosodiethylamine (NDEA), N-nitrosopyrrolidine (NPyr) and N-nitrosomorpholine (NMOR), in Sprague-Dawley female rats. Based on the difference between the amount of nitrosamines inhaled and exhaled, they estimated an absorption rate by inhalation of about 70%. In humans, considering the dead spaces in the lung, the absorption fraction average should be the same as in rats. For example, the fraction of absorption, as measured in volunteers exposed by inhalation to methanol is about 79% (Sedivec et al., 1981) (methanol has chemical characteristics similar to those of NDMA in terms of its water solubility and volatility in the air).

Distribution of NDMA in the mammalian organism

NDMA is miscible in water and has a low octanol/water partition coefficient (log K_{oe}: -0.57), its fraction of storage in adipose tissue is low. In regards to the pharmacokinetics, non-ionized molecules of low molecular weight and soluble in water tend to move freely across biological membranes and be distributed in the body fluids or in highly vascularized organs and tissues and in the extravascular fluid. One expects such behavior for NDMA.

No study of the distribution of NDMA or its metabolites has been carried out in humans. However, the following studies conducted in animals exposed intravenously and orally, confirm the distribution in the fluids of all tissues in the body of mammals.

- In mice, radioactivity was detected 15 minutes after administration of an intravenous dose of ^{14}C-NDMA. It was higher in the liver, lung and kidney, suggesting the presence of metabolites bound to macromolecules in these tissues (Johansson and Tjalve, 1978; Daugherty and Clapp, 1976).
- In rats exposed to an oral dose of 5 mg NDMA/kg/day for 4 weeks and sacrificed thereafter, Anderson et al. (1986) reported the presence of NDMA in the blood, liver, kidney, lung and brain.
- In pregnant Syrian hamsters, two hours after a subcutaneous dose of 12.5 mg/kg, NDMA was detected in maternal blood, placenta, amniotic fluid and fetus (Althoff et al., 1977).

No studies on distribution of NDMA and its metabolites have been performed following inhalation exposure in animals or humans.

Elimination

Following an intravenous dose of 0.5 or 1 mg/kg bw in Beagle dogs, Gombar et al. (1987) observed that the removal of NDMA was rapid and occurred in two phases. During the first phase, the blood level decreased with a half-life of 19 minutes, and during the second phase

with a half-life of 73 minutes. At a dose of 5 mg/kg bw administered orally (fractional absorption 93%), the blood kinetics clearly showed a saturation of the metabolism of NDMA. NDMA is excreted in the urine as metabolites and as a small unchanged part, and by the pulmonary route in the form of carbon dioxide resulting from the degradation of formaldehyde formed by biotransformation of NDMA.

> *From a toxicological point of view, such an elimination rate (short half-life) implies that NDMA does not accumulate in the body after repeated daily exposure over long periods.*

The observations of Gombar et al. (1987) show a saturation of NDMA metabolism beyond the dose of 1 mg/kg bw. With the assumption that the cancer induction risk would be related to metabolites of NDMA, the authors conclude that, beyond this dose, the carcinogenic effects would not be increased at a rate proportional to increasing dose.

> *In the workplace, at the NDMA concentrations usually observed in the air (a few µg/m^3), there will be no saturation of metabolism of NDMA molecules in humans.*

Pharmocodynamics analysis. biotransformation and mechanisms of action

NDMA biotransformation pathways

The biotransformation of NDMA has been studied *in vitro* and *in vivo* in animals. This biotransformation is presented schematically in Figure 2.

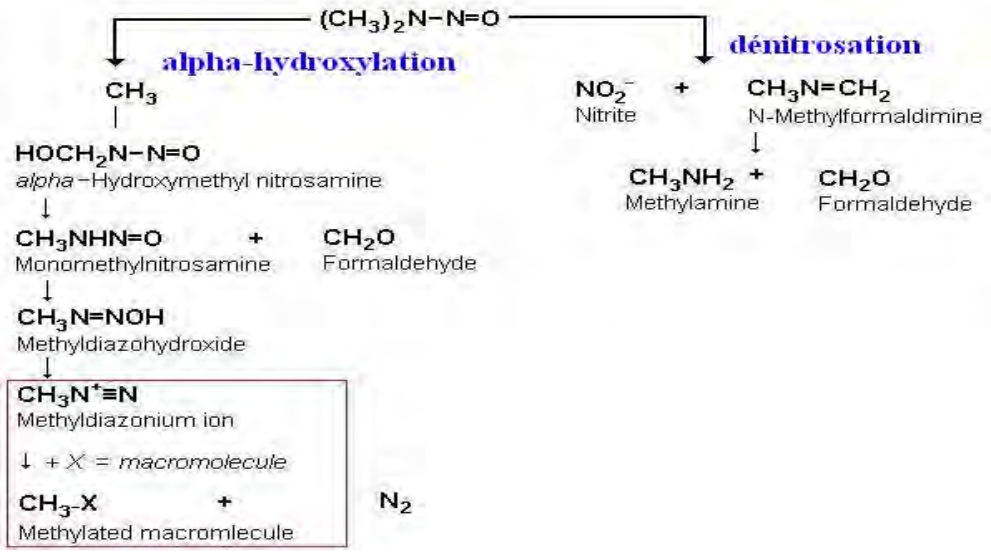

Figure 2 Metabolism of NDMA (from Liteplo and Meek, 2002)

Biotransformation follows two distinct pathways: one leading to a hydroxylation of NDMA and the other a denitrosation (Liteplo and Meek, 2002). Both routes would start with a common molecule, CH3(CH2)N-N=O resulting from the metabolism of NDMA by a mechanism dependent on the cytochrome P450 2E1 (Meskar et al., 2001).

There is a consensus in the scientific community that the carcinogenic effects of NDMA are caused by some of its metabolites rather than by NDMA itself (Boucheron et al., 1987; EPA, 1988; ASTR, 1989; Deal et al., 1989; Belinsky et al., 1990). This metabolism exists predominantly in the liver, kidneys and lungs.

The metabolism of NDMA which follows the path of hydroxylation produces a methylating agent, the methyldiazonium ion (Bamborschke et al., 1983; O'Connor et al., 1982; Pegg et al., 1981; Pegg and Hui, 1978; Stumpf et al., 1979). The methylating agent would form adducts with DNA, some of which could induce genetic damages (mutations and fragmentation of chromosomes) at the origin of these cancer cells (Lotlikar et al., 1975; Czygan et al., 1973).

Denitrosation is considered to be the deactivation pathway of the carcinogenic potential of NDMA (Keefer et al., 1987). In rats, the proportion of NDMA molecules metabolized via the denitrosation path would be significant: about 21.3% according to Streeter et al. (1990) and 29% according to Burak et al. (1991).

Thus, in theory, the risk of cancer depends on the relative importance of the route of hydroxylation in the total metabolism of NDMA. In humans, these proportions are not known; however, measurement of methylamine in the urine demonstrates the existence of this pathway.

Mechanism of action of the carcinogenic effect of NDMA

Methylation of DNA by NDMA was the subject of several studies (Bamborschke et al., 1983; O'Connor et al., 1982; Pegg et al., 1981; Pegg and Hui, 1978; Stumpf et al., 1979). It occurs at several positions on the DNA molecule, including positions N^1, N^3 or N^7 of the deoxyadenosine, N^3, N^7 or O^6 of the deoxyguanosine, N^3 of the deoxycytidine and O^2 or O^4 of the thymidine and tend to form adducts with DNA. In the literature, the adducts are named according to the position of the methyl group, a result of methylation, and the basis on which it occurs. For example, the adduct resulting from methylation of deoxyadenosine at N^7 is called N^7-adenosine adducts and that resulting from methylation of deoxyguanosine at O^6 is called O^6-methylguanine adduct.

The major adduct formed is N^7-methylguanine. It represents about 65% of all adduct compounds formed following exposure to NDMA. The O^6-methylguanine adduct represents about 7% of all adducts formed. Other DNA adducts formed in smaller quantities include N^3-methyladenine and O^4-methylthymine.

Among all these adducts, O^6-methylguanine and O^4-methylthymine attracted the attention of several researchers (Bamborschke et al., 1983; O'Connor et al., 1982; Pegg et al., 1981; Pegg and Hui, 1978; Stumpf et al., 1979). They have been shown *in vitro* to cause fragmentation of DNA molecules.

> *In vitro studies have shown that several human tissues can metabolize NDMA (liver, kidney, lung and brain). Human cells metabolize nitrosamines in a manner similar to that observed in animal cells. In human lymphocytes, the same DNA adducts as those observed in experimental animal studies are detected* (Reh et al., 2000).

This observation *in vitro* and *in vivo* of an association between the rate of DNA mutation and the presence of O^6-methylguanine adducts in several animal species exposed to NDMA has led researches to investigate whether such a link would exist in humans (Reh et al., 2000; Oesch and Klein, 1992).

Note that the formation of specific adducts with DNA in a cell is accompanied by the induction of repair enzymes for these adducts or adducts of the same family and, in principle, in all cell types affected. Thus, the formation of O^6-methylguanine adducts causes the induction of repair enzymes O^6-alkylguanine-DNA alkyltransferase (AGT).

The formation of these adducts can also be caused by nitrosamines other than NDMA, whether from endogenous or exogenous sources, and by all the chemicals that can produce DNA methylation, and this is true for other types of adducts listed above. This makes it very difficult to analyze a relationship between exposure to a specific agent and the concentration of these adducts in some cells of the body (eg, lymphocytes readily available in the blood).

For example, Reh et al. (2000) have examined whether there was an association between exposure to nitrosamines in a rubber gaskets manufacturing industry for automotive and the concentration of adducts N^7-methylguianine, O^6-methylguanine and AGT repair enzyme present in blood lymphocytes of 85 workers.

They divided the workers into five categories of average exposure to total nitrosamines: 17 subjects in category I (4.44 ± 2.15 µg/m^3), 15 subjects in group II (2.97 ± 1.16 µg/m^3), 20 subjects in category III (2.32 ± 1.37 µg/m^3), 12 subjects in category IV (0.67 ± 0.69 µg/m^3) and 21 subjects in the control group, category V (undetectable).

- The concentration of N^7-methylguianine adducts was the highest in all groups, however, no significant difference was detected between groups after controlling for age. In each group, the concentration varied greatly between individuals (eg, in the control group, it ranged from 0.1 to 128.2 adducts per 107 deoxyguanosine DNA bases.
- No difference in the average concentration of repair enzyme AGT between groups was observed.

Regarding O^6-methylguanine adducts, out of 78 tests performed, only 38 were positive. The concentrations ranged from undetectable to 12.7 x 10^7 deoxyguanosine DNA bases. By performing a nonparametric statistical test, they noted a positive association between the air concentration of total nitrosamines and the proportion of positive tests by category. Between the first three categories, the result was almost identical (about 60% positives), whereas in the last two categories the percentages were respectively 40% and 30%. Based on these results, the authors conclude that the demonstration of this association provided further evidence on a possible link between the presence of O^6-methylguanine adducts and cancer.

Comments on Reh et al. (2000) article

The authors did not control for confounding factors, such as smoking and diet, very important factors in the risk of cancer. It would have been interesting to control these factors to see if they have an effect on adducts production. In addition, the authors provided no data on the

concentrations' distribution of O^6-methylguanine adducts by category, they only compared the rates of exceeding the detection limit of the measurement of adducts.

Yet, it would have been interesting to see whether in any of the groups most at risk (groups I and II), the average values of concentrations above the detection limit was significantly higher than that of less exposed groups (groups III and IV).

In this type of study, the measure of the adducts repair enzyme caused by O^6-methylguanine, the enzyme O^6-methylguanine-DNA alkylthyltransferase (AGT), is based on the assumption that it would play a critical role in the ability to develop tumors following exposure to NDMA. But in the study of Reh et al. (2000), there were no significant differences in the average concentration of AGT between groups. However, the extent of individual variability varied by a factor of more than 1,000 in each group. Does this mean that some individuals would be 1,000 times more likely than others to contract cancer? It seems that many other factors may modulate the individual response in mammals exposed to possible carcinogens. We list some below:

- Camus et al. (1990) showed that the composition of the diet plays a role in the rate of DNA methylation by NDMA in the liver of rats. Indeed, the concentration of O^6-methylguanine in the liver was six times higher in rats given NDMA incorporated during six weeks in a high-fat diet than in those who received the same dose of NDMA in a low-fat diet.
- Meskar et al. (2001) found that in hepatocytes from alcoholic subjects, the activity of cytochrome P450 2E1 involved in the hydroxylation metabolism of NDMA was multiplied by a factor of three to five times, which would theoretically increase the formation of O^6-methylguanine.

One must be very cautious in interpreting data from this study and remember that carcinogenesis is the result of a stochastic process, which means that the physiological changes that cause such a health problem (mutations) are primarily the result of chance. Indeed, even if some people have characteristics that make them more genetically susceptible to suffer from cancer, partly because of differences in activation, the deletion or repair of DNA mutations that occur on specific genetic sites required to cause cancer would be the result of chance. Thus, unlike most non-carcinogenic effects, if two subjects are equally exposed to a carcinogen and have the same degree of genetic susceptibility, cancer could occur in a person and be absent in the other.

Based on this information at the individual level, measuring the concentration of these metabolites has little utility. However, in an epidemiological study in terms of research, this type of analysis could allow to confirm the hypothesis of their involvement in the increased incidence of cancer with exposure to nitrosamines.

3.2.3 Critical analysis of epidemiological studies in Germany

In the section "Historical analysis of cancer risks for workers in the rubber industry", we have seen that on the basis of epidemiological studies published before 1998, there was consensus on a high degree of evidence of an excess mortality from cancers among workers

in this industry worldwide. Bladder cancer, leukemia, cancers of the stomach and lung were most frequently observed. Thus, before 1998, published studies did not allow to estimate the contribution of nitrosamines to these cancers, no more than that of other contaminants in the industry.

The experts argued that leukemia is predominantly associated with exposure to solvents, and bladder cancer, to aromatic amines.

Regarding the risk of stomach cancer and lung cancer, a doubt remained that nitrosamines are the cause and the experts suspected factors other than nitrosamines. German researchers have attempted to verify the link between these cancers and various contaminants in the work environment in the rubber industry in Germany, including nitrosamines, asbestos, talc and carbon black. They initially established a cohort of more than 11,000 employees working in various sectors of the industry in Germany (Weiland et al., 1996).

Subsequently, for this specific cohort, several research protocols were developed and implemented, in stages, to verify the existence of a causal link between certain cancers and various contaminants. The results of these investigations have been published by Weiland et al. (1998), Straif et al. (1998) and Straif et al. (2000a and b). We describe these investigations below by summarizing and analyzing their results and conclusions.

Weiland et al. study, 1996

Towards the end of the 1980s, the possibility of an increased risk of morbidity and mortality from cancer among workers in the rubber industry in Germany became an increasing source of concern for occupational physicians. In fact, no epidemiological data on workers in this industry was available in Germany. Since the need for documenting the health status of workers in this sector was also raised by the industry, it was decided in 1990 to initiate a significant epidemiological investigation that could ultimately provide a better understanding of the cancer risk factors present in this industry, so as to eliminate them. The study, published by Weiland et al. (1996), presented the methodology used to conduct that investigation. In addition, it examined the risk of death from cancer in the German rubber industry in connection with time-related factors such as the year of hiring of deceased subjects and the time elapsed between that date and their death.

In 1992, over 50% of the approximately 95,000 employees working in the rubber industry were employed in businesses with fewer than 1,000 employees, of which approximately 70% were blue collar workers. For practical reasons, the cohort created by Weiland et al. (1996) came from companies with more than 1,000 employees for which available data enabled the identification of potential members of the cohort and the reconstruction of their work history with adequate quality. In pursuit of these criteria, five plants belonging to three companies were selected during a pilot phase lasting nine months. These five plants were located in three different German states. The authors wanted to create a cohort whose power would be sufficient to detect excess cancer mortalities, even for cancers with rare incidence.

Methodology

The cohort was composed of male workers who were: (a) active after January 1st 1981, or (b) retired and alive on January 1st 1981. It thus included 11,663 workers, of which 7,536 were active and 4,127 retired. The subjects had to have worked at least one year in one of these plants and be younger than 85 years on January 1st 1981. The formation of a sub-cohort of retired subjects provided an opportunity to assess the health impact of hazards in the early years of the creation of this industry.

The majority of the 4,127 members of this sub-cohort began their employment before 1960 in these factories, including 500 before 1930. As to the sub-cohort of subjects still active after January 1st 1981, most were recruited between 1950 and 1969. The cohort study has generated a total of 110,512 person-years at risk, including 31,260 attributable to workers who retired before January 1981 and 79,252 to workers still active after this date.

The option of following the mortalities that occurred after 1981 is based on the following reasons. First, in most German states, the law requires keeping death certificates for a period of 11 years and their destruction thereafter. Secondly, 1981 was the first year for which electronic data were mandatorily compiled for each worker by health insurance companies. Plant archives documents and data from insurance companies allowed to obtain 99.7% of the information on work history of all members of the cohort and about 97% of causes of death of 2,719 workers who died during the 11 years of follow-up. Death rates analyzed in sub-cohorts based on the year of hire, the year of termination and duration of employment were compared with observed death rates during this period among men in the same age groups in the national German population.

The specific cancers examined are: cancers of the pharynx, esophagus, stomach, colon, rectum, liver and gall bladder, pancreas, larynx, lung, trachea and bronchi, pleura, prostate, bladder, brain and other organs of the nervous system, lymphatic system and leukemia.

In addition, several causes of death other than cancer were analyzed. The coding of diseases used by insurance companies is the same as that of the country (ICD-9). The authors studied the relative risk of death of these two sub-cohorts by comparing the observed number of deaths attributable to various causes studied to the number expected in the national German population after standardizing (controlling) for gender and age. So these relative risks are expressed as SMR. Three types of analysis were conducted:

1. Global SMR for each cause of death for each sub-cohort.
2. The risk of death from cancer was also analyzed in each sub-cohort according to year of hiring (< 1950; 1950-1959 and ≥ 1960) for both sub-cohorts studied.
3. Finally, for both sub-cohorts studied, the risk of death from cancer was analyzed according to the number of years elapsed between the year of workers' death and the year they were hired in the industry (< 10 years; 10-19 years and ≥ 20 years).

For retired workers, 0.1% belong to the category of < 10 years, 4.3% in the 10-19 years category and 95.6% in the category of over 20 years. Among active workers, 9.5% belong to the category of < 10 years and 17.7% to the 10-19 years, and 72.8% to the category of over 20 years.

Results summary of the Weiland et al. (1996) study

The excess mortalities observed in the study cohort, irrespective of year of hire and the number of years between year of death and year of hire, are distributed as follows:

- *Retirees and active groups combined*, statistically significant excesses of mortalities were observed for:
  - the total of all causes of death including cancers (SMR 108; 95% CI: 104-112);
  - the total of all deaths from cancers analyzed (SMR 111; 95% CI: 103-119);
  - the combined group of death from cancers of the lung, trachea or bronchi (SMR 130; 95% CI: 115-147);
  - no excess mortalities for other cancers analyzed.
- *Among the subgroup of retirees, a significant excess of mortalities was observed for:*
  - the total of all causes of death including cancers (SMR 113; 95% CI: 108-118);
  - total of all cancers analyzed (SMR 114; 95% CI: 104-124).
- *Among deaths from specific causes of cancer, only the following cancers were in excess in a statistically significant manner:*
  - the combined group of cancers of the lips, oral cavity or pharynx (13 cases for an SMR of 193: 95% CI: 103-331);
  - the combined group of cancers of the lung, trachea and bronchi (163 cases and SMR 134; 95% CI: 114-156);
  - cancer of the pleura (13 cases and SMR 533; 95% CI: 284-912);
  - leukemia (22 cases and SMR 164; 95% CI: 103-249).
- *Among the subgroup of workers who were still active after January 1st 1981:*
  - only an excess of mortalities due to the combined group of cancers of the lung, trachea and bronchi was observed (94 cases and SMR 124; 95% CI: 100-152).

After analysis for both sub-cohorts, the risk of death according to the year of hire (< 1950, 1950-1959 and ≥ 1960) and the number of elapsed years between the year of workers' death and the year they were hired in this industry (< 10 years 10-19 and ≥ 20 years), the observations are:

1. The observed excess cancer mortalities between January 1st 1981 and December 31st 1991 are in the group "lung, trachea and bronchus" cancers, cancer of the pleura, cancer of the pharynx, cancer of the bladder and leukemia.
2. The statistically significant excess of mortalities attributable to the "lung, trachea and bronchus" group of cancers is observed in the sub-cohort of retirees and in the total cohort (total of retired before 1981 and active after 1981). The significant excess of mortalities occurred more than 10 years after the year of employment termination of affected individuals, i.e., among the sub-group of 10-19 years in the sub-cohort of retirees

(SMR 218: 95% CI 100-413) and among the subgroup of ≥ 20 years of the overall cohort (SMR 129: 95% CI 113-146) and of the sub-cohort of retirees (SMR 132, 95% CI 112-155). In the sub-cohort of subjects still active in 1981, no statistically significant excess of mortalities attributable to this group of cancers is observed in the various subgroups stratified by year of hire and by the number of years between the year of death of workers and the year they were hired in this industry.

3. Statistically significant excesses of mortalities from cancer of the pleura (SMR 555, 95% CI: 295-950) and leukemia (SMR 171, 95% CI 107-259) were also observed in the sub-cohort of retirees of over 20 years after beginning of employment. Note that these excesses appeared only in subjects hired before 1960, in the two sub-groups (< 1950 and 1950-1959).

4. Regarding the deaths caused by cancer of the pharynx, 12 of the 13 deaths occurred more than 20 years after beginning of employment, including seven in sub-cohort of retirees and five in the cohort of subjects who were still active in 1981. However, an excess of mortality appears only in the group of retirees (seven cases observed for SMR 255: 95% CI 102-526). Indeed, in the sub-cohort of active subjects, 20 years after beginning of employment, there is no increased risk (five cases for SMR 93: 95% CI 30-216).

5. Deaths from cancers of the bladder are in excess in the total cohort among subjects hired after 1960. During this same period, in both sub-cohorts, the risk of death is increased, but the excesses observed are not significant. Among workers hired before 1960, no excess is observed. When the authors analyzed the data according to years elapsed between the date of death and the beginning of employment, no excess was visible. There seems to be some increase in the subclass of 10-19 years, but this increase is not significant. In the subclass of 20 years and over, there is no increase.

6. Note that no worker among those hired after January 1st 1981 (n = 3,721) has died of cancer during the period between January 1st 1991 and December 31st 1991, although 2.8 deaths were expected according to the national rate. Among these workers, 20 died from other causes compared with 23 expected deaths in the German population.

Comments in connection with the observations of Weiland et al. (1996) study

1. For all cancer mortalities in excess in this large German cohort (the "lung, trachea and bronchus" group of cancers, cancer of the pleura, cancer of the pharynx, bladder cancer and leukemia), it is clear that the risk mainly affects the sub-cohort of retirees. Indeed, excesses for all these cancers are observed only in the sub-cohort of retirees before 1981. Excesses are also observed in the overall cohort for the "lung, trachea and bronchus" group of cancers, bladder cancer and leukemia. Kogevinas et al. (1998) had already noted in their review of epidemiological studies that in the rubber industry, since the 1950s and more intensively after 1970, measures were implemented to prevent impacts on workers health and safety: local ventilation, substitution of toxic chemicals by less hazardous substances, etc., which could explain this observation.

2. One must ask whether the absence of significant excess in the active group after 1981 is due to a too short latency for onset of cancer deaths. Among the sub-cohort of retired subjects 1,918 of all deaths from cancer (N = 1976) occurred in the subgroup of those

who died 20 years after the date of hire. This subgroup represented 95.6% of person-years at risk in this sub-cohort (29,869/31,260 pers.-years). Of the sub-cohort of subjects still active after January 1st 1981, 640 of the 727 deaths that occurred between January 1st 1981 and December 31st 1991 are from the subgroup of subjects hired more than 20 years before their deaths; that subgroup represents 72.8% of person-years at risk in this sub-cohort (57,681/79,252 pers.-years). The vast majority of people belonging to this sub-group are older than 50. This difference of 22.8% (95.8%-72.8%) of person-years at risk between the two sub-cohorts in people for whom the time elapsed between the date of hire and cancer deaths would be more than 20 years, may lead to an underestimation of the real risk of the sub-cohort of active subjects compared to retirees.

3. Another point to consider is the effect of choice of the observation period of deaths, between January 1st 1981 and December 31st 1991, on the outcome. Recall that practical constraints prevented the authors from obtaining data for the previous years. However, we can question the impact of not having data prior to 1981. Given that subjects in the sub-cohort of retirees before 1981 were employed in this industry before 1960 and that those from the sub-cohort of active members were hired mainly after 1960, it is very likely that the absence of data on deaths that occurred before 1981 may have resulted in an underestimation of the risk for the sub-cohort of retirees. However, regarding the cohort of workers who were still active after 1981, it is unlikely that this factor has had a significant effect on the outcome, considering the long latency between exposure to risk factors and the occurrence of cancers associated with this risk and the time of occurrence of deaths from these cancers. Indeed, for those subjects, death would be expected to occur after 1981.
4. The excess mortality from bladder cancer in the overall cohort after 1960, but not before that date, raises questions. Indeed, it is difficult to understand this observation. Even after that date, there is no excess observed in the subgroup of 20 years elapsed between the occurrence of cancer death and the beginning of employment in this industry. In Great Britain, before 1960, an excess risk of bladder cancer was associated with β-naphthylamine exposure, an aromatic amine, (IARC, 1982). However, discontinuation of its use has subsequently shown a gradual and significant decrease in the incidence of this cancer. Has such a substance been used for a short period in the German industry?
5. Regarding leukemia in the last update of the IARC in 1998, experts who reassessed the risk of cancer in the rubber industry concluded that these cancers were associated with exposure to solvents such as benzene (IARC, 1998).
6. In regards to deaths from cancer of the pleura, the not significant SMR greater than 100 in the sub-cohort of subjects active after 1981 prevents us, on the basis of this study, to draw a clear conclusion on the risk for this sub-cohort. The studies analyzed below, which were conducted by the same team of German researchers, will shed new light on this cancer.

Studies of Weiland et al., 1998 and Straif et al., 1998

These two articles focused on the relationship between mortality from specific cancers, workplace characteristics (work area and job title) and the time factor (year of beginning of employment and the number of years employed in companies) among workers in the two

sub-cohorts studied by Weiland et al. (1996) (active workers after January 1st 1981 and retired workers before that date.) The study of this relationship is divided into two parts according to the types of cancers analyzed.

In the first study (Weiland et al., 1998), the authors verified if there was a relationship between workplace characteristics and an excess of mortalities from cancers of the respiratory system (larynx, lung and pleura).

In the second study (Straif et al., 1998), they analyzed the risk of excess mortalities from all non-respiratory cancers. In addition, a detailed analysis focused specifically on cancers of the pharynx, esophagus, stomach, colon, prostate, bladder and leukemia.

In both studies, the time factor (year of beginning of employment and the number of years working at companies) was taken into account in the analysis.

Work areas in which employees of the five plants under study have worked, have been analyzed from archival documentation relating to plant operations and classified into six categories:

I. Preparation of materials
II. Production of various technical rubber products other than tires (eg, molding seals used in automotive and electrical appliances
III. Production of tires
IV. Storage and distribution (or delivery) of finished products
V. Maintenance
VI. Other

For each of these categories, the cohort was stratified by year of hire (≥ 1960, 1950-1959 and < 1950) and the number of years in employment (1-9; ≥ 10 and total ≥ 1 year).

The work history for all members of the cohort was reconstructed at more than 99.7%. The number of person-years (p-y) at risk by category was established as follows:

- Category I: 25,406 p-y
- Category II: 45,000 p-y
- Category III: 30,432 p-y
- Category IV: 8,206 p-y
- Category V: 30,724 p-y
- Category VI: 14,722 p-y

In the various categories, 40% to 50% of person-years are from the age group of workers aged ≥ 60 years. All cohort members were employed between 1911 and 1981 with 75% after 1950. In categories I to V, the number of employees who worked more than 10 years in these plants exceeds the number of those who worked less than 10 years.

Recall that in the global study by Weiland et al. (1996), cancers for which excess mortalities were observed are all cancers combined, cancers of the lung, pleura, group of cancers of the oral cavity or lips or pharynx, bladder and leukemia.

Thus, in the studies of Weiland et al. (1998) and of Straif et al. (1998), we should see how these cancers are distributed among the various categories I to VI. Of course, it is not impossible that an excess of mortality from cancer other than those observed in previous studies appear in one or more of the categories studied by Weiland et al., (1998) and Straif et al., (1998). We summarize below the observations of statistically significant excesses in these two studies. For the reader who wants more information on the observations of cancer for which there was no mortality increase, we refer to articles referenced at the end of this document (Weiland et al., 1998; Straif et al., 1998).

Summary results for the Weiland et al. (1998) study

This study examines the link between job characteristics and excess mortality from cancers of the respiratory system among workers in the German cohort.

- A statistically significant excess of mortalities from *cancers of the larynx* is observed in category I (preparation of materials):
  a. Among *workers hired after 1960* (3 cancers were observed for SMR 534: 95% CI 110-1558);
  b. Among *workers who worked more than 10 years* (5 cancers were observed for SMR 330: 95% CI 107-769).
- Excess mortalities from lung cancer are observed in categories I (preparation of materials), II (production of various technical rubber products other than tires) and V (maintenance):
  a. Category I: (80 cancers for SMR 162: 95% CI 129-202);
  b. Category II: (99 cancers for 134: 95% CI 109-163);
  c. Category V: (67 cancers SMR 131: 95% CI 102-167).

For this type of cancer, in contrast to cancer of the larynx, the number of cases was sufficient to have good precision on the estimates:

- Excess of deaths from cancer of the pleura are also observed in categories I, II and V:
  a. Category I: (4 cancers for SMR 448: 95% CI 112-1146);
  b. Category II: (7 cancers for SMR 505: 95% CI 202-1040);
  c. Category V: (5 cancers for SMR 554: 95% CI 179-1290).

Note that the categories affected by cancer of the pleura are the same as those affected by lung cancer.

- No significant excess of mortalities from cancers of the respiratory system is observed in categories III (tire production), IV (storage and delivery of finished products) and VI (other).

Conclusion of the Weiland et al. (1998) study

The authors believe that excess mortality from cancers of the lung and pleura would be due to exposure to asbestos present in certain environments in the rubber industry.

Moreover, according to these authors, the excess mortality from laryngeal cancer observed in category I could also be associated with exposure to asbestos. They note that recently (before 1998), laryngeal cancer associated with exposure to asbestos is a recognized occupational disease in Germany. They also mention that the excess mortality from cancers of the lung and pleura in subjects hired after 1960 suggests that this phenomenon is not exclusively a problem of the distant past. They indicate that it was not possible to clearly associate these excesses to a specific factor. However, they state that their hypothesis will be verified in future analysis, based on exposure to specific risk factors.

Summary results of the Straif et al. (1998) study

This study examines the link between job characteristics and deaths from cancers other than those affecting the respiratory system among workers in the German cohort.

- An excess of mortalities from *cancers of the pharynx* is observed:
  a. In category II (production of various technical rubber products other than tires, such as the production of moldings of seals used in the automotive and appliance industries) in subjects hired after 1960 (4 cases observed for SMR 375: 95% CI 102-960).
  b. In category IV (storage and distribution of finished products) among all employees who worked more than a year in one of these plants (3 cases observed for SMR 486: 95% CI 100-1419).
- An excess of mortalities from *cancer of the esophagus* is observed only in category III (production of tires): 11 cases observed for SMR 227: 95% CI 114-407.
- No excess mortalities from *cancers of the stomach and colon* was observed, whatever the category studied.
- An excess of mortalities from *prostate cancer* is observed only in category V (maintenance) among all workers (27 cases observed for SMR 152: 95% CI 100-221).
- Excess of deaths from *bladder cancer* are found among employees hired after 1960:
  a. In category III (tire production), 4 cases observed for SMR 412: 95% CI 115-1078).
  b. In category IV (storage and distribution of finished products), 5 cases observed for SMR 514: 95% CI 168-1207.
  c. In category V (maintenance), 7 cases observed for SMR 336: 95% CI 135-692.
- Excess mortalities from leukemia were observed in category I (preparation of materials) and II (production of various technical rubber products other than tires) in subjects hired between 1950 and 1959 and who worked more than 10 years in the industry.

Conclusion of the Straif et al. (1998) study

It is clear that several types of cancers are associated with working in the rubber industry. However, the role of exposure to a family of specific substances such as nitrosamines or a mixture of substances will be subject to further analysis on their part. Which will be done later (Straif et al., 2000a and b). The results from this work will be presented and discussed below.

Comments regarding the studies of Weiland et al., 1998 and Straif et al., 1998

Regarding the excess of mortalities from cancer of the larynx in zone I (preparation of materials), there is a small number of cases observed, which explains the lack of precision in the results that are reflected by large confidence intervals at 95%. It is therefore difficult to conclude that there is a clear link between excess and working in the rubber industry.

However, there is a very clear correlation between the excess of mortalities from cancers of the lung and pleura of those in categories I (preparation of materials), II (production of various technical rubber products other than tires) and V (maintenance). This suggests a common cause.

A statistically significant excess of mortalities from *cancers of the pharynx* is observed:

a) In category II (production of various technical rubber products other than tires, such as the production of sealing strips used for automobiles and appliances) in subjects hired after 1960 (4 cases observed for SMR 375: 95% CI 102-960). However, stratifying according to employment duration (1-9; ≥ 10 years and ≥1 year) for these four workers who died from this cancer, in each stratum the total number of deaths is too low for the excess of mortalities observed to be statistically significant.

b) In category IV (storage and distribution of finished products), among all workers who worked more than a year in one of these plants (three cases observed for SMR 486: 95% CI 100-1419). Two of the three cancers observed occurred among workers hired between 1950 and 1959 and the other occurred in an individual hired after 1960. Two of the affected individuals belonged to the stratum of workers who worked more than 10 years in the industry and the other to the stratum of subjects who worked between one and nine years.

Recall that in the study of Weiland et al. (1996) discussed earlier, we saw that the excess of mortalities from cancers of the lung, pleura and pharynx were observed in the cohort of retirees before 1981, among workers mostly hired before 1960 in the rubber industry and more 20 years after the date of commencement of their employment in this industry.

Study of Straif et al. 2000a

In this study, the authors analyze the relationship between estimated exposure to nitrosamines (NDMA and NMOR) and the risk of excess mortalities from specific cancers. Other potentially carcinogenic nitrosamines such as N-diethylamine (NDEA) and N-nitrosopyrrolidine (NPyr), also present as contaminants in the rubber industry, were not measured.

Note that the original cohort established by Weiland et al. (1996) has been reduced from 11,663 to 8,933 workers in the study of Straif et al. (2000a), because only workers hired after January 1 1950 were considered. So the subjects eliminated were part of the sub-cohort of retirees before 1981.

The exposure to nitrosamines in this cohort of 8,933 workers was estimated using two exposure categories predefined by the authors, but the criteria on which these categories were based upon are not explained. Each of these exposure categories was stratified into three subclasses (low, medium, high) and subgroups' relative risk "Medium and high exposure" was estimated in relation to the subgroup of low exposure (RR = 1). To facilitate interpretation of results, we present the definition of these categories by the authors.

Table 11 Categories of exposure to nitrosamines defined by Straif et al. 2000a

Category 1:	- **Low**:	< 1 year between 2,5 µg/m^3 and 15 µg/m^3
	- **Medium**:	between 2,5 and15 µg/m^3 duration > 1year
	- **High**:	≥ 1 year at more than 15 µg/m^3
Category 2:	- **Low**:	< 0,5 years at less than 2,5 µg/m^3
	- **Medium**:	between 2,5 et 15 µg/m^3 duration ≥ 0,5 to < 10 years
	- **High**:	≥ 10 years at more than 15 µg/m^3

Results

The results of this study are presented in Appendix 2. In this Appendix, for the medium and high sub-categories of the two exposure categories listed in table 11, the relative risk (RR) of death for all cancers studied was calculated by comparing the death rates observed with that of the corresponding low subcategory. In this study, we note the absence of excess mortalities from lung cancer and stomach cancer in relation to exposure to nitrosamines NDMA and NMOR in these industries.

In contrast, statistically significant excesses of mortalities were observed and are due to:

- Cancers of the esophagus in the "high exposure" subclass of exposure categories 1 (RR 7.3: 95% CI 1.9 to 27.8) and 2 (RR 9.1: 95% CI 2.1 - 38.8).
- Cancers of the pharynx in the "high exposure" subclass of exposure category 1 (RR 4.1: 95% CI 1.0 to 17.2).
- "Lip, oral cavity and pharynx" cancer group in the "medium exposure" (RR 3.6, 95% CI 1.1 to 11.7) and "high exposure" (RR 5.1, 95% CI 1.2 to 20.6) subclasses of category 2 and the "high exposure" subclass of category 1.

Comments on the Straif et al. (2000a) study

In this study, only workers hired after 1950 were retained for the analysis. In our opinion, this has the effect of underestimating the risk for retirees because of greater exposure to various ambient contaminants before that date.

However, if we look at the risk of today's workers, the data from this cohort are certainly more representative than those that include workers hired before 1950. Ideally, in this context, it would have been preferable to have only workers hired after 1970, however, the low latency would prevent from obtaining results that are representative of the risk for this population.

In this type of industry in Germany, measured levels of nitrosamines were not available before 1979. The estimation of exposure since that date has been conducted on the basis of measurements made in the early 1980s as part of a broader study of environmental monitoring in the rubber industry, including many plants where the cohort was formed. Retrospective exposure to nitrosamines prior to 1979 was estimated based on the judgments of industrial hygienists and experts who had participated in these measures and had a good knowledge of technologies and processes used in this industry decades earlier. Straif et al. (2000a) reported several observations that we consider very relevant to our analysis of the various sources of exposure to nitrosamines:

a. The highest levels of nitrosamines in the air were detected in vulcanization areas where N-nitrosodiphenylamine was used as a delaying agent (NDMA: 15-140 µg/m³) (replaced in the early 1980s) and in the drying zone with salt baths (NDMA: 1-130 µg/m³) that used amine derivatives as accelerators, except in those baths where peroxide accelerators were used instead.

b. Concentrations of nitrosamines were detected in the vulcanization zone and subsequent stages on the production lines in which neither N-nitrosodiphenylamine nor salt baths with peroxide were used (NDMA: 1 to 4.5 µg/m³).

c. In workplace areas preceding the vulcanization, such as handling of powders and chemicals, mixing, etc., where nitrosamines concentrations were low (NDMA: 0.1-2 µg/m³).

There are many overlaps between exposure's subclasses and categories in which these excesses were observed in this study:

a. Individuals in the cohort who worked more than 10 years in these plants all belong to one or the other of the "high exposure" subclasses in categories 1 and 2 (Table 11).

b. A number of workers belonging to the subclass "medium exposure" of exposure category 2 (Table 11) may have been exposed to a cumulative dose higher than that of some workers belonging to the "high" subclass of category 1. For example, an individual who had worked for nine years by being exposed to an average concentration of 12 µg/m³ of nitrosamines (a subject included in the medium subclass of category 2) would have been exposed to a cumulative dose greater than that of a worker exposed to an average concentration of 20 µg/m³ of nitrosamines during one year (subject included in the "high" subclass of category 1.

c. Also note that the range of the "medium exposure" subclass of exposure category 1 (between 2.5 and 15 µg/m³ with a duration > 1 year) is included in the "medium exposure" subclass of exposure category 2 (between 2.5 and 15 µg/m³ with a duration of ≥ 0.5 years to < 10 years). Thus, we must conclude that these two types of cancers are associated with exposures of more than one year at (NDMA + NMOR) concentrations of more than 2.5 µg/m³.

Based on these data, we will try to determine a threshold for excess mortalities from cancers of the pharynx and esophagus in the study cohort in relation to exposure to nitrosamines (LOAEL) in this cohort.

1. Mortalities from cancer of the pharynx were in excess in the "high exposure" class of category 1 but this excess was not statistically significant. In the "high exposure" class of category 2, an excess was observed, but this excess was not statistically significant. This observation suggests that a certain number of cancers were added for exposures of less than 10 years at concentrations > 15 µg/m³. The total number of deaths from cancer of the pharynx observed in this cohort of 8,933 workers was only nine cases.

By analyzing the article Straif et al. (1998) in which the authors analyzed the risk of death from cancer (other than cancers of the larynx, lung and pleura) in the initial cohort of 11,633 workers based on six categories of work areas, we note that:

- There were 20 deaths out of 11,633 workers from cancer of the pharynx, whereas in the study Straif et al. (2000a), only nine cases were found for 8,933 workers. Since only subjects hired after 1950 are part of that study, it is concluded that 11 of the 20 cancer deaths occurred among workers hired before 1950;
- Among the 20 deaths of the Straif et al. (1998) cohort study, nine deaths occurred among employees who worked in this industry for over 10 years and 11 among those who worked during the period of one year to nine years.

  Note that there is no correspondence between the cases listed in this paragraph and those in the preceding paragraph. The same numbers (9 and 11 cases) are the result of chance;
- Not statistically significant excesses of mortalities from cancer of the pharynx, observed in the “medium and high exposure” subclasses of exposure category 2, incite caution. ("medium exposure" subclass: RR 3.54: 95% CI 0.7-19.9 and "high exposure” subclass: RR 4.7 95% CI 0.6 to 35.5). Of course, the wide range of the 95% CIs is an indication of a lack of power associated with the scarcity of cancer cases (*only nine in total*), the result of a lack of precision. But since a significant increase was observed in the "high exposure" class of category 1, it is reasonable to wonder what would have happened in category 2 if the cohort had been larger, given the overlap between categories (Category 2: medium exposure duration of $\geq$ 0.5 years to < 10 and between 2.5 and 15 µg/m^3, and high exposure $\geq$ 10 years at more than over 15 µg/m^3).

By cross-referencing data from the distribution of the number of cohort members by work area and date of hire with those of the distribution of the number of person-years at risk for different age groups of workers in the six categories of work areas (see Weiland et al., 1998), we conclude that the average time spent by workers in these plants varied between 9 and 10 years depending on the types of work areas to which they belonged.

> *Thus, in the rubber industry in Germany, at least in the cohort analyzed, we conclude that the LOAEL for cancer of the pharynx corresponds to an average concentration of NDMA + NMOR between 2.5 µg/m^3 and 15 µg/m^3 of air for an average exposure period of about 10 years*.

2. An excess of mortalities was observed for the "lip, oral cavity and pharynx" group of cancers in the "high exposure" subclasses of categories 1 (RR 3.9, 95% CI 1.4 to 11.1) and 2 (RR 5.1, 95% CI 1.2 to 20.6) and in the "medium exposure" subclass of exposure category 2 (RR 5.1, 95% CI 1.2 to 20.6).

   Recall that this subclass is defined as follows: exposure duration ≥ 0.5 years to < 10 years at concentrations ranging between 2.5 and 15 µg/m³. Of the 17 cancer deaths attributable to this group, nine were caused by cancers of the pharynx as already mentioned, which may explain much of the excess observed in this “lip, oral cavity and pharynx” group. Because of the excess observed in the average exposure subclass in the exposure category 2, we cannot completely exclude a carcinogenic effect due to nitrosamines for cancers of the lip and oral cavity at concentrations between 2 5 and 15 µg/m³. However, if a significant excess of one of these cancers had been observed, it would be surprising that the authors would not mention that.

   > *Thus, in the rubber industry in Germany, at least in the cohort analyzed, we conclude that the LOAEL for the "lip, oral cavity and pharynx" group of cancers corresponds to an average concentration between 2.5 µg/m³ to 15 µg (NDMA + NMOR)/m³ of air for an average exposure period of about 10 years.*

3. For cancer of the esophagus, 13 deaths were observed in this cohort for 8,933 workers hired after 1950. An excess of mortalities is observed in the "high exposure" subclass of the two exposure categories. In category 1, RR = 7.3 (95% CI 1.9 to 27.8) and in category 2, RR = 9.1 (95% CI 2.1 to 38.8). No excess is observed in the "medium exposure" subclass of the two categories.

In the overall analysis of the risk of death from cancer in the rubber industry performed by Weiland et al. (1996), in which neither exposure to specific substances nor work areas were considered, out of a total of 21 deaths from cancer of the esophagus, no statistically significant excess of mortalities was observed in the initial cohort of 11,633 workers (including individuals hired before 1950).

Moreover, among workers hired after 1960, i.e., most of the subjects from the cohort of active workers after 1981, no excess of mortality, not even non significant, from cancer of the esophagus was observed. These data clearly demonstrate that the risk of death from that type of cancer was much higher among employees who worked in this industry before 1950.

Given the improvements made between 1950 and 1970 to reduce workers’ exposure to various contaminants in this industry, it is likely that the risk has gradually declined during that period.

However, one cannot ignore the association observed by Straif et al. (2000a) between the risk of death from cancer of the esophagus and exposure to concentrations above 15 µg (NDMA + NMOR)/m³ in the cohort of workers hired after 1950. In the study by Straif et al. (1998), where the risk of excess mortalities from cancers were analyzed according to the working areas of the original cohort (11,766 workers), an excess of mortalities from cancer of the esophagus was observed in category III (tire production: 11 cases observed for a SMR of

227, 95% CI 114-407). In the latter case, retirees who had been hired before 1950, however, were part of the study.

Recall that in the large study in rats by Peto in 1991, NDEA was associated with an increased incidence of cancer of the esophagus, but NDMA did not affect this organ. In that study, animals were exposed orally. It is know that NDEA is always present in all types of rubber industry, but at levels generally lower than NDMA (Oury et al., 1997). It is difficult to understand why cancer of the esophagus was found in excess only in the tire industry. Was NDEA present in greater concentrations in this type of industry before 1960? Given that in humans, the mechanisms of action of nitrosamines are the same as those observed in rats, it is possible that the concentrations of NDEA were high during this period, which would explain the observed excesses for exposures to levels greater than 15 µg (NDMA + NMOR)/m^3. Unfortunately, NDEA molecule was not measured by Straif et al. (2000a).

> *Thus, in the rubber industry in Germany, at least in the cohort analyzed, we conclude that the LOAEL for cancer of the esophagus corresponds to an average concentration greater than 15 µg (NDMA + NMOR)/m^3 of ambient air for an average exposure period of about 10 years.*

4. Although not statistically significant, the increase in RR (ranging from 3.5 to 6) for cancers of the "brain and CNS" in the "medium and high" exposure subclasses for the 2 exposure categories analyzed by Straif et al. (2000a) drew our attention. In the study cohort, it should be noted that there were only six deaths from these cancers, and these six deaths were divided into the two "medium and high" subclasses for each category of exposure. A priori, the lack of precision due to the rarity of these cancers prevents us from reaching a conclusion on a potential causal link.

Thus, to better understand this problem, we returned to earlier studies by Weiland et al. (1996 and 1998). In these studies, there was no increase in mortalities from brain cancer in both sub-cohorts (pre-1981 retirees and members still active after this date) taken together, i.e., without stratification for year of hire or for the time elapsed between the year of hire and death or, for the number of years employed by this industry. The SMRs for each sub-cohort and the total cohort were all below 100. Depending on the year of hire, the SMRs were below 100 for the strata of years of hire of workers affected by these cancers beyond 1950 (i.e. 1950-1959 and $\geq$ 1960 strata).

For the stratum of workers hired before 1950, only the SMR of the sub-cohort of retirees was increased, but this increase was not significant (SMR 156, 95% CI: 32-456). Again, this observation suggests that the risk was more important before 1950. Based on this analysis, we conclude that a causal link between exposure to nitrosamines and cancers of the brain and CNS cannot be totally excluded in this cohort. The RRs observed are possibly the result of chance.

Study of Straif et al., (2000b)

In this study, the authors sought to identify factors that may have led to excess mortalities from cancers of the lung, stomach and larynx, already observed in the rubber industry in Germany and elsewhere in the world. To do this, they estimated the distribution of the cohort

of 8,933 workers (the same as those in the study by Straif et al., 2000a) based on worker exposure to nitrosamines, asbestos, talc and carbon black.

Summary results of this study

- After controlling for confounding factors (asbestos, talc and carbon black), nitrosamines were not found to be associated with any of the cancers analyzed: lung, stomach and larynx.
- The excess mortalities from lung cancer is associated with exposure to asbestos: medium exposure category compared with low (RR = 1.3, 95% CI 0.9 to 1.9) and high exposure category compared to low (RR = 2.0, 95% CI 0.9-4.1).
- An excess of mortalities from stomach cancer is associated with combined exposure to talc and asbestos.
- Deaths from cancer of the larynx appear to correlate with lung cancer; however the authors noted that the low number of deaths does not allow to draw a clear conclusion on a specific causal link.

Comment

Given the high degree of specificity between pleural cancer and exposure to asbestos and the observation by Weiland et al. (1998) of a strong correlation between the excess of mortalities from cancers of the lung and pleura in categories I (preparation of materials), II (production of various technical rubber products other than tires) and V (maintenance), the link observed by Straif et al. 2000b between asbestos and lung cancer seems plausible.

Note that for cancer of the bladder and for leukemia, researchers have not attempted to verify the link with specific factors. We suppose that they did not put into question the conclusions of the IARC experts on the causal link between aromatic amines and bladder cancer and between benzene and leukemia.

3.2.4 Analysis of a British study on workers who began their employment after 1982 in the rubber industry

The study, published by Dost et al. in 2007, covers only workers (men and women) employed recently in the rubber industry in Great Britain. The cohort studied consisted of workers from 41 plants located in England, Wales and Scotland. All the plants were members of the British Rubber Manufacturers Association (BRMA), which represents the tire industry or of the British Rubber and Polyurethane Products Association (BRPPA), which represents the rubber products industry in general (GRG: General Rubber Goods). The cohort is composed of 7,561 men and 1,090 women who worked in one of these plants for at least a year between 1982 and 1991. The authors compared the incidence of cancer deaths that occurred between 1983 and 2004 in this cohort with the expected national rate.

Results

The standardized mortality ratios (SMR) for lung and stomach cancers were lower than those expected in the general population, for both genders. We note, however, that these ratios are based on a small number of cases. For lung cancer, among men, there were 22 deaths observed for an SMR of 93, and in women, only two deaths for an SMR of 70. For stomach cancer, there were four deaths in men for with an SMR of 86 and none in women.

Note that the authors controlled for smoking with three classes (smoker, ex-smoker and non-smoker of many years).

For these two types of cancer, they conclude that it is reassuring to note that these results go in the opposite direction to those generally observed in this type of industry. However, the limited latency and low cancer rates call for caution before drawing definitive conclusions.

In the rubber products industry in general, the authors observed a significant increase in deaths from multiple myeloma and this on a small number of deaths recorded among men (observed 5, SMR 385) and women (observed 2, SMR 952). This result is rather unexpected and the authors indicate that they should be interpreted with caution. However, they add that the high number of deaths from multiple myeloma may reflect a risk factor related to unknown occupational activities in the industry of rubber products, excluding tires.

Comment

First, this study did not include information on:

- Age of the subjects involved, their exposure and history of employment prior to 1982;
- Age of the industries, their activities, the type of technology used, etc.

In our opinion, on the methodological level, we would call this type of study exploratory. It can help identify potential problems and raise some speculations that deserve to be verified by further studies. Hopefully, this work will have some continuation in order to elucidate this potential problem.

4 DISCUSSION AND CONCLUSION

In this analysis, we have seen that several animal studies have shown that nitrosamines, including NDMA and NDEA, were carcinogenic and that carcinogenic effects were observed for oral and respiratory exposures. In other words, the types of cancers induced have a correlation with the entry route. Indeed, the major cancers observed after oral exposure are cancers of the esophagus (associated with NDEA) and liver cancer (associated with NDMA and NDEA). Regarding inhalation exposures, it is the nasal-pharyngeal cancers (related to NDMA only) and the lung cancers that were observed.

Several studies suggest that the cancers are initiated by certain metabolites of nitrosamines, which have the power to produce DNA mutations through an oxidative mechanism. Human cells metabolize nitrosamines in a manner similar to that observed in animal cells and in vitro studies have shown that metabolites of NDMA produced in rodents are also produced in humans. Several human tissues may metabolize NDMA (liver, kidneys, lungs, brain). Moreover, in human lymphocytes, the same DNA adducts as those observed in experimental animal studies are detected (Reh et al., 2000). Like rodents, humans readily absorb nitrosamines via the oral and respiratory tracts.

Some studies show large differences between species in the capacity of biotransformation and repair of mutations induced by various toxic substances. Inter-individual differences also exist within species. This may explain, at least in part, the important differences between species and intra-species regarding the susceptibility to cancer. However, even if the risk varies between species, the presence of mechanisms inducing mutations leads to the conclusion that this risk cannot be nil.

Based on these observations, it was reasonable to anticipate that NDMA is carcinogenic to humans.

Furthermore, epidemiological investigations have been conducted to test this hypothesis. In their latest update on the assessment of cancer risk in the rubber industry in 1998, experts commissioned by the IARC established that in this industry, there was a sufficient degree of evidence as to the existence of a causal connection between bladder cancer and the presence of aromatic amines and between leukemia and the existing solvents. They also indicated that data from epidemiological studies suggested the possibility of a link between the preparation, mixing and molding of rubber products and the increase in lung and stomach cancers.

They also mentioned that even if the excesses of cancers of the colon, prostate and lymphomas were occasionally observed in some studies, the data were inadequate to establish a causal link with the workplace. However, according to the authors of this assessment, published epidemiological studies had several limitations that warrant caution in their conclusion.

For example, the lack of measured concentrations of contaminants in the workplace did not allow establishing a causal link with specific risk factors. In addition, confounding factors potentially associated with the types of cancers observed were not controlled in these studies. A meta-analysis by Kogevinas et al. (1998) reached similar conclusions.

In 1990, in Germany, it was decided to initiate an important epidemiological investigation that would examine the cancer risk factors that exist in the rubber industry. This epidemiological study have led to the publication of five articles between 1996 and 2000 following a cohort of some 11,000 workers employed between 1910 and 1991 in five different facilities manufacturing various rubber products such as tires and gaskets used in automotive and appliance industries.

In the German studies, the cancers studied were: cancers of the lip, oral cavity, pharynx, esophagus, stomach, colon, rectum, liver and biliary cavities, pancreas, larynx, lung, prostate, bladder, kidney, brain, lymphoma and leukemia. In general, with the exception of cancer of the larynx, the excesses observed were those identified by experts of the IARC and by Kogevinas et al. 1998. The German studies clarified the causal link between cancer and carcinogens in the rubber industry.

Based on our analysis of all these studies, we determined that in the German cohort, the minimum level for which an excess risk of mortality from cancers associated with exposure to nitrosamines, corresponds to an exposure for about 10 years at an average concentration that is between 2.5 µg/m³ to 15 µg/m³ of the total (NDMA + NMOR). It should be noted however that this threshold (LOAEL) is based on the observation of two very rare cancers i.e., cancers of the pharynx and esophagus, in a cohort of 8,933 workers hired after 1950. For these two cancers, statistically significant excesses were observed only for exposures lasting more than a year at concentrations above 15 µg (NDMA +NMOR)/m³. The excesses observed for exposures between 2.5 and < 15 µg (NDMA +NMOR)/m³ were not statistically significant. However, the lack of power leads us to caution, especially since the average duration of exposure of these workers was about 10 years.

Obviously, the ability to accurately detect a statistically significant LOAEL depends on the number of cases covered by the study and the number of deaths during the period of observation. Unfortunately, it is impossible to determine a threshold of no effect within this range (2.5 µg/m³ to 15 µg/m³).

It is also impossible to verify if the workers exposed for a period longer than the average duration of exposure (10 years) were the ones who have mainly contributed to excess mortalities observed, even though theoretically this hypothesis seems more likely.

Considering that in the rubber industry in general, the combination "NDMA + NMOR" represents approximately 85% of total nitrosamines (Oury et al., 1997), we conclude that for this cohort, the value of a LOAEL based only on NDMA concentration would be similar to that obtained with the "NDMA + NMOR" combination.

The results of the study of Peto et al. (1991), conducted by exposing rats orally, suggests the presence of a threshold daily dose without effect, which seems quite high (about 100 µg NDMA/kg bw).

Recall that the oral absorption fraction of NDMA in rats is about 8% only whereas in humans a fraction of at least 80% is expected, which is 10 times higher than in rats. In the study by Klein et al. (1999), where rats were exposed by inhalation, carcinogenic effects occurred at the lowest daily dose administered (10 µg NDMA/kg bw). Thus, animal studies do not allow setting up a LOAEL and a NOAEL. It is nonetheless reassuring to note that for the concentrations of NDMA measured in the warehouse of finished rubber products in the Eastern Townships, the workers' average daily dose (about 0.4 µg NDMA/kg bw) for an average NDMA concentrations in the air of about 3 µg NDMA/m³, is much lower than the dose used in the animal studies cited above. Moreover, the species of rats used in these studies seem more sensitive than humans in contracting the cancers observed by the authors.

Cancer is the result of several specific DNA mutations that are not fixed by repair mechanisms that exist in human cells, leading to the conversion of a malignant tumor. The risk of specific mutations (unrepaired) depends on several personal factors (phenotype of the enzymes involved in metabolizing toxic substances and cellular repair, health status) and external factors (intensity and duration of exposure to carcinogens).

Indeed, since the induction of cancer in a given tissue requires the presence of several mutations different and specific to this cancer (between four and six mutations according to geneticists) (Klug et al., 2006), and since the appearance of each specific unrepaired mutation is due to chance, the risk of the presence of all these mutations increases with time and with the degree of exposure to the carcinogen that induces such mutations. Thus, in regards to the risk of cancer associated with a mutagen, the cumulative dose seems to be the best indicator of risk. Therefore, for chronically exposed workers, the lower the average daily dose of exposure to nitrosamines, the more negligible the risk attributable to this exposure will be.

A given type of cancer is rarely due to a single factor. In other words, it is rather rare that the portion attributable to a particular risk factor approaches 100%. A well-documented exception is the "pleural cancer and exposure to asbestos" association. For example, in the general population, cancers of the pharynx and esophagus are associated with risk factors other than nitrosamines (alcohol, tobacco and unknown causes). Thus, in order to accurately assess the proportion of cancers attributable to exposure to nitrosamines in the workplace, the contribution from all other causal factors should be eliminated. In methodological terms, those facts should be taken into account to control their effects when developing the study protocol.

In theory, the effect of this approach is to compare a population exposed to nitrosamines to an unexposed population, which would otherwise be exposed in an almost identical manner to the other risk factors that can cause these cancers. In the study by Straif et al. (2000a) the rate of deaths observed in the exposed cohort was compared with that expected in the German population without controlling for risk factors like alcohol and cigarette consumption.

However, they controlled for gender and age factors in their comparison. In fact, the lack of control for smoking and alcohol is like considering that the workers were tobacco and alcohol consumers in proportions similar to those of men with the same age distribution in the German general population. This is possible, but unproven. Thus, uncertainties remain about the causal association between exposure to nitrosamines and cancer of the pharynx and esophagus in this study. Unfortunately, the possibility that the observed excess mortalities are mainly due to nitrosamines cannot be excluded.

Despite some limitations, the German studies at least have the merit of being those that best explored the link between excess cancer mortalities observed in the rubber industry and various risk factors in this industry.

5 RECOMMENDATIONS

Nitrosamines exposure levels measured in the storage facilities of finished rubber products in the Eastern Townships are at the lower end of concentrations associated with statistical increase of mortality by cancer in the German workers cohort, exposed for an average of about 10 years to nitrosamines ranging from 2.5 to 15 µg/m³ of air.

Since the careers of some workers may extend over a period lasting up to 40 years, it seems reasonable that the average ambient concentration of NDMA for an exposure of 40 years be limited to less than 2.5 µg NDMA/m³ of air to protect the health of all workers.

Thus, the German standards (1 µg/m³ for total nitrosamines), those proposed in Switzerland (1 µg/m³ for NDMA) and in the Netherlands (0.2 µg/m³) for application in the rubber industry seem reasonable. Indeed, according to our analysis, excess cancer mortalities attributable to nitrosamines in the rubber industry for an exposure period of 40 years at an average concentration equal to or less than 1 µg NDMA/m³, 8 hours per day and 40 hours per week seem insignificant. It is unfortunately impossible to prove 100% that the risk is nil, since no epidemiological evidence exists for such prolonged average exposure at this average daily concentration.

Therefore, in light of our analysis, we recommend that efforts be made to reduce worker exposure to total nitrosamines to daily average concentrations below 1 µg/m³ of air (8 hours per day, 40 hours per week).

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APPENDIX 1

OCCUPATIONAL EXPOSURES OBSERVED IN THE RUBBER PRODUCTS INDUSTRY IN VARIOUS COUNTRIES

Table 1a

Reference	**Jonsson LS, Lindh CH, Bergendorf U, Axmon A, Littorin M, Jonsson BA. N-nitrosamines in the southern Swedish rubber industries: exposure, health effects, and immunologic markers. Scand J Work Environ Health 2009 May;35(3):203-11.**				
Country	**Sweden**	**Companies' activities**	**Manufacturing of various rubber products**		
Type of study	**Environmental assessment of nitrosamines exposure levels; estimation of the risk of occurrence of various non-specific symptoms and changes in levels of biomarkers in relation to these levels**				
	Process or job description	**Sampling type**	**N**	**Nitrosamine**	**Concentrations range (µg/m³)**
Results	**Unspecified occupations in 8 plants**	**Personal**	**96**	**NDMA**	**< Limit of detection (LoD)-28**
				NDEA	**< LoD-4.6**
				NDBA	**< LoD-0.53**
				NMOR	**< LoD-2.0**
				NPIP	**< LoD-2.8**
				NPYR	**< LoD-1.9**
	Compression and injection vulcanization	**Personal**	**63**	**Total nitrosamines**	**< LoD-2.9 (Median: 0.24 µg/m³)**
	Curing by hot air/microwaves/fluid-bed vulcanization	**Personal**	**15**	**Total nitrosamines**	**< LoD-13 (1.3 µg/m³)**
	Salt bath vulcanization	**Personal**	**16**	**Total nitrosamines**	**< LoD-36 (4.2 µg/m³)**
Commentaries	• **Nitrosamines with the most results < LoD are NMOR, NPIP and NPYR** • **The eight plants were considered as 12 areas of exposure, the authors have assigned a category of exposure to each of these areas depending on the concentrations of total nitrosamine: low (< 0.3 µg/m³), intermediate (between 0.3 and 3 µg/m³) and high (> 3 µg/m³)** • **According to this categorization, exposure was considered low in 5 areas, intermediate in 5 five areas and high in 2 areas** • **52% of 63 employees working in compression/injection had a low exposure category versus 48% with intermediate exposure** • **For the 15 workers involved in the curing by hot air/microwaves/fluid-bed, the proportions were: 13% low, 47% intermediate and 40% high** • **For the 15 workers involved in salt bath vulcanization, the proportions were: 13% low, 13% intermediate and 75% high** • **The authors acknowledge that the measured exposure levels are high enough and that efforts should be made to reduce them. However they were unable to establish an association between symptoms or biological markers and measured levels of nitrosamines.**				

NDMA: N-nitrosodimethylamine NDEA: N-nitrosodiethylamine NPIP: N-nitrosopiperidine
NPYR: N-nitrosopyrrolidine NDBA: N-nitrosodi-n-butylamine NMOR: N-nitrosomorpholine

Table 1b

Reference	**Iavicoli I, Carelli G. Evaluation of occupational exposure to N-nitrosamines in a rubber-manufacturing industry. J Occup Environ Med 2006 Feb;48(2):195-8.**				
Country	**Italy**	**Companies' activities**	**Manufacturing of rubber drive belts for automotive engines**		
Type of study	**Environmental assessment of nitrosamines exposure levels and biological monitoring (urine)**				
	Process or job description	**Sampling type**	**N**	**Nitrosamine**	**Results (µg/m³)**
Results	**Various unspecified occupations (factory 1)**	**Personal**	**-**	**NDMA**	**4/15 > LoD [0.07, 0.07, 0.08 and 0.35 µg/m³]**
				NDEA	**15/15 < LoD**
				NDBA	**15/15 < LoD**
				NMOR	**15/15 < LoD**
	Various unspecified occupations (factory 2)	**Personal**	**-**	**NDMA**	**1/9 > LoD [0.10 µg/m³]**
				NDEA	**2/9 > LoD [0.08 and 0.10 µg/m³]**
				NDBA	**1/9 > LoD [0.06 µg/m³]**
				NMOR	**9/9 < LoD**
	Various unspecified occupations (factory 3)	**Personal**	**-**	**NDMA**	**5/5 > LoD [Mean ± SD: 0.14 ± 0.07 µg/m³]**
				NDEA	**5/5 > LoD [0.15 ± 0.03 µg/m³]**
				NDBA	**5/5 < LoD**
				NMOR	**4/5 > LoD [0.16 ± 0.05 µg/m³]**
Commentaries	• **Majority of air samples < 0.06 µg/m³(LoD)** • **Urinary nitrosamines detected in 8/34 workers only and these levels are not influenced by sources not related to work** • **The highest exposures were observed among workers performing vulcanization**				

Table 1c

Reference	**Reh BD, DeBord DG, Butler MA, Reid TM, Mueller C, Fajen JM. O(6)-methylguanine DNA adducts associated with occupational nitrosamine exposure. Carcinogenesis 2000 Jan;21(1):29-33.**					
Country	**USA**	**Companies' activities**	**Manufacturing of rubber vehicle sealing strips and other rubber products for automobiles**			
Type of study	**Environmental assessment of nitrosamines exposure levels and comparison with concentrations of DNA adducts detected in blood following exposure**					
	Process or job description		**Sampling type**	**N**	**Nitrosamine**	**Mean ± standard deviation (µg/m³)**
Results	**Salt bath lines operators - sealing strips manufacturing (plant A – category I)**		**Personal**	**17**	**NDMA**	**2.54 ± 1.37**
					NPIP	**1.59 ± 0.73**
					NMOR	**0.30 ± 0.15**
	Workers not near the salt bath lines (plant A – category II)		**Personal**	**15**	**NDMA**	**1.22 ± 0.60**
					NPIP	**1.05 ± 0.27**
					NMOR	**0.70 ± 0.70**
	Workers not involved in manufacturing but working near or in the area of sealing strips manufacturing (plant A – category III)		**Personal**	**20**	**NDMA**	**1.27 ± 0.85**
					NPIP	**0.88 ± 0.51**
					NMOR	**0.17 ± 0.13**
	Workers not involved in manufacturing and working far from the area of sealing strips manufacturing (plant A – category IV)		**Personal**	**12**	**NDMA**	**0.42 ± 0.52**
					NPIP	**0.21 ± 0.24**
					NMOR	**0.05 ± 0.05**
	Workers of Plant B manufacturing other automotive rubber parts (category V)		**Personal**	**21**	**NDMA**	**< LoD (0.01 µg/m³)**
					NPIP	**< LoD**
					NMOR	**< LoD**
Commentaries	• **Range of total nitrosamine concentrations in categories I to III: 0.4 à 9.3 µg/m³ with 54% over 2.5 µg/m³ (the German occupational standard for rubber vulcanizing and processing industries)** • **The study did not establish a link between the environmental exposure levels and the adducts concentrations; nevertheless, some hypotheses are suggested by the authors**					

Table 1d

Reference	**Oury B, Limasset JC, Protois JC. Assessment of exposure to carcinogenic N-nitrosamines in the rubber industry. Int Arch Occup Environ Health 1997;70(4):261-71.**					
Country	**France**	**Companies' activities**	**Manufacturing of various rubber products**			
Type of study	**Occupational exposure assessment to nitrosamines**					
	Process or job description		**Sampling type**	**N**	**Nitrosamine**	**Results**
Results	**All departments combined (mixture, salt bath vulcanization, UHF vulcanization, curing by hot air, finishing, warehousing and other)**		**Predominantly area**	**180**	**Total nitrosamines**	**Median: 3.54 µg/m³ [0.07-104.37 µg/m³]**
	Salt bath vulcanization		**Predominantly area**	**96**	**Total nitrosamines**	**Median: 11.24 µg/m³ [0.61-104.37 µg/m³]**
	Attendant, reception of bands at the end of vulcanization line		**Unknown**	**-**	**Total nitrosamines**	**Maximum value: 20 µg/m³**
Commentaries	• **Only the results of samples in the vicinity of salt baths during the manufacture of sealing strips have been detailed in this table** • **The five nitrosamines identified are: NDMA, NDEA, NDBA, NPIP, NMOR** • **No results > 2.5 µg/m³ for mixing and some results (13%) for finishing and (7%) for storage** • **Some recommendations regarding methods of prevention and control of exposure**					

Table 1e

Reference	**Oury B, Protois JC. N-nitrosamines volatiles dans l'industrie du caoutchouc : évaluation de l'exposition professionnelle sur trente-six lignes de vulcanisation continue. Cahiers de notes documentaires 1997;(168):441-52. (in French)**					
Country	**France**	**Companies' activities**	**Manufacturing of rubber products**			
Type of study	**Environmental characterization of exposure in relation to three types of continuous vulcanization (bath salts, UHF and hot air)**					
	Process or job description		**Sampling type**	**N**	**Nitrosamine**	**Mean ± standard deviation (Min-Max)**
Results	**Various jobs related to salt bath vulcanization**		**Area**	**59**	**Total nitrosamines**	**8.1 ± 6.6 µg/m³ (0.5-22.1)**
	↓ →→→	**Upon exiting the extruder**	**Area**	**12**	**Total nitrosamines**	**4.4 ± 3.5 µg/m³ (0.5-10.3)**
	→→→	**Near salt bath lines**	**Area**	**26**	**Total nitrosamines**	**5.8 ± 4.9 µg/m³ (0.6-20.3)**
	→→→	**Rinsing of streamlined**	**Area**	**9**	**Total nitrosamines**	**12.2 ± 8.8 µg/m³ (1.5-22.1)**
	→→→	**Nearby equipment (drilling, marking, folding, cutting, etc.)**	**Area**	**12**	**Total nitrosamines**	**13.9 ± 5.3 µg/m³ (1.9-21.6)**
	Attendants assigned to various tasks in connection with salt bath vulcanization		**Personal**	**14**	**Total nitrosamines**	**10.3 ± 7.5 µg/m³ (0.3-26.1)**
	Reception and storage of moulded strips exiting from the salt bath lines		**Area**	**21**	**Total nitrosamines**	**13.8 ± 9.9 µg/m³ (0.8-34.6)**
	Attendants at the reception and storage of moulded strips exiting from the salt bath lines		**Personal**	**13**	**Total nitrosamines**	**18.9 ± 13.0 µg/m³ (0.6-42.9)**
Commentaries	• **The authors indicate that the following nitrosamines have been identified in samples according to the type of accelerators used in the various vulcanization baths: NDMA, NDEA, NDBA, NPIP and NMOR, and that concentrations of NDMA are often the highest** • **They pay particular attention to the reception/storage of moulded strips exiting from the salt bath lines that are "still more or less hot". They state that "at this stage, the concentrations of pollutants are even more important as there is freshly vulcanized rubber accumulation."** • **They conclude that "(...) the generation of nitrosamines is not instantaneous but continues beyond the stage of vulcanization (...) The movement and storage in the open section of freshly cured products are sources of high emissions (of nitrosamines), particularly if the products have hollow part and if they are subjected to drilling or cutting."**					

Table 1f

Reference	**Reh BD, Fajen JM. Worker exposures to nitrosamines in a rubber vehicle sealing plant. Am Ind Hyg Assoc J 1996 Oct;57(10):918-23.**					
Country	**US**	**Companies' activities**	**Manufacturing of rubber vehicle sealing strips**			
Type of study	**Occupational exposure assessment to nitrosamines**					
	Process or job description		**Sampling type**	**N**	**Nitrosamine**	**Mean ± standard deviation (µg/m³)**
Results	**Salt bath line operators (All samples of NDPA and NDBA were undetected)**		**Personal**	**8**	**NDMA**	**4.28 ± 1.87**
					NDEA	**0.32 ± 0.26**
					NPIP	**2.05 ± 0.78**
					NPYR	**0.06 ± 0.02**
					NMOR	**0.11 ± 0.05**
	Salt bath line assistants (All samples of NDPA and NDBA were undetected)		**Personal**	**9**	**NDMA**	**4.41 ± 3.05**
					NDEA	**0.11 ± 0.06**
					NPIP	**2.11 ± 1.03**
					NPYR	**0.06 ± 0.03**
					NMOR	**0.15 ± 0.06**
	Salt bath line feeders (All samples of NDPA and NDBA were undetected)		**Personal**	**3**	**NDMA**	**1.59 ± 1.22**
					NDEA	**0.16 ± 0.15**
					NPIP	**0.70 ± 0.46**
					NPYR	**0.01 ± 0.003**
					NMOR	**0.07 ± 0.05**
	Moulding/finishing operators (All samples of NDPA and NDBA were undetected)		**Personal**	**8**	**NDMA**	**1.23 ± 0.40**
					NDEA	**0.10 ± 0.13**
					NPIP	**1.16 ± 0.47**
					NPYR	**0.04 ± 0.02**
					NMOR	**0.38 ± 0.83**
Commentaries	• **Area samples time-weighted averages at various locations of the plant were: (NDMA) 6.3 to 37.7 µg/m³ (NPIP) 3.9 to 7.6 µg/m³ (NMOR) 0.2 to 0.37 µg/m³ (NDEA) 0.16 and 0.38 µg/m³** • **The average results of six area samples near the drilling lines were: (NDMA) 23.20 ± 32.62 µg/m³ (NDEA) 0.05 ± 0.07 µg/m³ (NPIP) 4.24 ± 3.04 µg/m³ (NPYR) 0.13 ± 0.04 µg/m³ (NMOR) 0.23 ± 0.19 µg/m³** • **The salt bath lines are the main source of exposure; salt bath operators and assistants had the highest nitrosamine concentrations** • **Some rubber stocks contained dinitrosopentamethylene tetramine and appear to produce the highest nitrosamine concentrations while processed**					

Table 1g

Reference	**Spiegelhalder B, Preussmann R. Occupational nitrosamine exposure. 1. Rubber and tyre industry. Carcinogenesis 1983 Sep;4(9):1147-52.**						
Country	**Germany**	**Companies' activities**	**Manufacturing of various rubber products (tires, inner tubes, window seals for cars, shoe soles, hoses ...)**				
Type of study	**Portrait of occupational exposure to nitrosamines in various sectors in the manufacturing of rubber products in Germany**						
	Industry or process		**Job description**	**Sampling type**	**N**	**Nitrosamine**	**Concentrations range (µg/m³)**
Results	**Manufacturing of tires and general rubber goods**		**Raw material handling, weighing, mixing, milling, extruding, calendering**	**Personal and area**	**-**	**NDMA**	**0.1-2**
						NMOR	**0.1-9**
			Assembly and building	**Personal**	**-**	**NDMA**	**0.1-1**
						NMOR	**0.5-3**
	Salt bath curing		**Curing or vulcanizing**	**Personal**	**-**	**NDMA**	**1-130**
						NDEA	**0.1-5**
						NMOR	**0.1-3**
						NDPhA	**5-8**
	Manufacturing of window seals for cars		**Salt bath vulcanization**	**Process**	**-**	**NDMA**	**1-3.5**
						NMOR	**3-9**
	Manufacturing of tires and inner tubes		**Inspection and finishing**	**Process**	**-**	**NDMA**	**0.1-≤ 10**
						NMOR	**0.1-20**
			Storage and dispatch	**Process**	**-**	**NDMA**	**0.2-19**
						NMOR	**0.3-17**
Commentaries	• **It is difficult to separate precisely the data related to each sector of activity and type of process. The article provides a general picture of exposure to nitrosamines. Peak values in area samples of 1060 µg/m³ of NDMA and 4700 µg/m³ of NMOR were reported during the manufacturing of conveyor belts.** • **According to the authors, surveys undertaken in Germany between 1979 and 1983 showed that in the tire industry, NDMA and NMOR were detected in all cases, whereas in the general rubber goods, NDMA, NDEA, NDBA, NPIP and NMOR have been found.**						

NDPhA: N-nitrosodiphenylamine.

APPENDIX 2

RESULTS OF THE STUDY BY STRAIF ET AL. (2000A)

Table 1 Exposure to nitrosamines and mortality from cancer among workers (n = 8933) hired between 1950 and 1981 in the rubber industry (adapted from Straif et al. (2000a)

Cancer	ICD-9	Death	Exposure category 1*				Exposure category 2*			
			Medium		High		Medium		High	
			RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
All causes	000-999	**1429**	**1.2**	**1.1-1.4**	**1.3**	**1.1-1.4**	**1.2**	**1.0-1.5**	**1.4**	**1.0-1.8**
All cancers	140-208	444	1.2	0.9-1.5	**1.3**	**1.1-1.7**	**1.2**	**1.0-1.5**	**1.4**	**1.0-1.8**
Specific Cancers										
Lips, oral cavity and pharynx	140-149	17	0.8	0.2-4.1	**3.9**	**1.4-11.1**	**3.6**	**1.1-11.7**	**5.1**	**1.2-20.6**
Oral cavity	141,143-145	7	0.9	0.1-8.6	2.9	0.6-14.4	3.4	0.6-18.8	2.9	0.3-33.3
Pharynx	146-149	9	0.8	0.1-7.9	**4.1**	**1.0-17.2**	3.8	0.7-19.9	4.7	0.6-33.5
Esophagus	150	13	1.7	0.3-10.3	**7.3**	**1.9-27.8**	2.7	0.7-11.5	**9.1**	**2.1-38.8**
Stomach	151	44	0.8	0.4-1.8	1.2	0.5-2.5	0.9	0.5-1.8	1.2	0.5-3.2
Colon	153	21	0.4	0.1-1.7	1.5	0.6-3.8	0.6	0.2-1.8	1.5	0.5-4.7
Rectum	154	19	0.8	0.2-2.3	0.6	0.2-2.3	0.8	0.3-2.2	0.8	0.2-3.9
Liver, gallbladder	155-156	9	0.9	0.2-4.5	1.1	0.2-5.7	0.9	0.2-3.8	1.0	0.1-8.3
Pancreas	157	15	0.7	0.2-2.7	0.5	0.1-2.4	0.9	0.3-2.6	0.5	0.1-4.4
Larynx	161	8	0.4	0.0-3.1	0.4	0.0-3.0	0.5	0.1-2.3	0.0	
Lung	162	147	1.0	0.6-1.5	1.0	0.7-1.6	1.0	0.7-1.5	1.1	0.6-1.8
Prostate	185	26	1.4	0.5-3.8	2.2	0.9-5.6	1.6	0.7-3.7	2.1	0.7-6.2
Bladder	188	21	1.1	0.4-3.3	1.5	0.5-4.2	1.2	0.5-3.0	1.3	0.4-5.0
Kidney	189	10	1.2	0.3-4.7	0.4	0.0-3.5	1.0	0.3-3.6	0.0	
Brain, CNS	191-192	6	**3.9**	**0.3-42.6**	**6.0**	**0.6-57.6**	**5.1**	**0.6-45.6**	**3.5**	**0.2-56.2**
Lymphoma	200-203	14	2.0	0.7-6.2	0.3	0.0-2.8	2.0	0.7-5.9	0.0	
Leukemia	204-208	20	1.3	0.5-3.6	1.2	0.4-3.5	1.3	0.5-3.4	0.8	0.2-3.5

* Categories of exposure to nitrosamines (NDMA and NMOR)

Category 1: - **Low**: < 1 year between 2,5 µg/m^3 and 15 µg/m^3
- **Medium**: between 2,5 and 15 µg/m^3, duration > 1year
- **High**: ≥ 1 year at more than 15 µg/m^3

Category 2: - **Low**: < 0,5 year at less than 2,5 µg/m^3
- **Medium**: exposure between 2,5 and15µg/m^3, duration ≥ 0,5 year to < 10 years
- **High**: ≥ 10 years at more than 15 µg/m^3

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