Appendix I

Valorization Addendum
1. Valorization addendum

According to the graduation regulations of Maastricht University dated on 19th June 2014, an additional chapter, the Valorization Addendum, is needed for the dissertation of the Ph.D candidate. The definition of valorization is “the process of creating value from knowledge, by making knowledge suitable and/or available for social (and/or economic) use and by making knowledge suitable for translation into competitive products, services, processes and new commercial activities” (Maastricht promotie reglement, 2013). Therefore, in the next section, answers to the following four questions are outlined: 1) What is the social (and/or economic) relevance of our research results (i.e. in addition to the scientific relevance)?; 2) To whom, in addition to the academic community, are the research results of interest and why?; 3) Into which concrete products, services, processes, activities or other activities could our results be translated and shaped?; and to what degree can the results be called innovative?; 4) What will be the value of our research for future valorization?

1.1 Social Relevance

The current thesis reports on fundamental research, to further clarify the relationship between inflammation, exposure to genotoxic chemicals and their combined contribution to subsequent cancer risk. More specifically, the focus of this thesis is how inflammation can influence carcinogenesis by the chemical carcinogen benzo[a]pyrene (B[a]P). B[a]P is chosen as an example, because it is a widely studied genotoxic agent. However, with the development of human society, more than 10,000 chemicals have been produced each year, and some of them were identified and grouped as genotoxic and/or chemical carcinogen [1]. Therefore, exposure to genotoxic compounds seems inevitable for the general population. A chemical carcinogen is a compound that can directly or indirectly react with DNA, which could eventually cause genome mutations. It is generally accepted that more mutations will result in a higher risk of developing cancer. Dermal contact, intake or inhalation of such chemical carcinogens can lead to the formation of various cancers at different sites of the body, including lung, liver, breast, colon, stomach, skin, bladder, prostate and nose. Although it is not allowed to produce and use chemical carcinogens in consumer products, still they are generated naturally and presented in ambient environment, food, water and soil. One group of carcinogens is the polycyclic aromatic hydrocarbons (PAHs), which is a group of aromatic compounds found in natural sources and produced due to incomplete combustion of organic matter [2]. B[a]P is one of the best studied PAH and is considered to be classic example of PAHs that is widely present in human daily life, including cigarette smoke, diesel exhaust and barbecued meat products. Due to the fact that exposure is inevitable for humans, the human body developed a system to guard against all sorts of harmful exposures. For example, the body can detoxify harmful compounds via metabolism, which convert toxic compound into less toxic ones that can be excreted out of the body. Even though there is damage to DNA, cells can often repair DNA damage or undergo apoptosis dependent on the exposure dose. However, unsuccessful detoxification or unrepaired DNA damage will lead to changes in gene expression and mutations in certain genes that can drive carcinogenesis. Until now, it is estimated that chemical carcinogens are responsible for approximately 41% of the worldwide cancer incidence and 42% of cancer death [3, 4].

With a deeper and more profound understanding of carcinogen induced cancer development, scientists found out that there are many risk factors that contribute to the susceptibility of part of the population to carcinogens. Known risk factors are age,
genetics, and lifestyle. Currently, another risk factor namely “inflammation” has attracted attention and it was suggested to play an important role in chemically induced carcinogenesis. Inflammation is a powerful physiological response to defend the human body against intruders, such as pathogens, chemicals, or irritants, as well as to help damaged tissue healing by removing cell debris and rebuilding tissue [5]. However, once the inflammation persists, chronic inflammation will be developed, and chronic inflammation is responsible for 20% of related cancers [5]. Moreover, recent epidemiological studies have found that, the combination of inflammation and chemical carcinogen exposure increased the risk of cancer even further; for example, COPD patients are at risk of developing lung cancer and the risk is further increased in patients who are smoking.

Thus, we have now realized that exposure to carcinogens induces carcinogenesis, inflammation induces carcinogenesis, and the combination of carcinogen exposure and inflammation even further increases the health risks. According to the NIH national cancer institute database, inflammation and carcinogen-induced diseases account for around 166.1 deaths per 100,000 persons each year [6]. Although exposure to environmental chemicals is often unavoidable, inflammation is a condition against which there are many potential medical remedies. However, the mechanism of how inflammation contributes to the development of chemically induced cancer remains unclear. More knowledge about this mechanism could thus help people with chronic inflammatory diseases to prevent the development of cancer as a secondary disease. This may be of particular importance when treatment of chronic inflammatory diseases increases the life span of subjects, which also increases the chance of getting cancer. The studies described in this thesis can give important leads for further research on the prevention of cancer, which still is an enormous societal burden.

1.2 Target groups

There are multiple potential target groups besides the academic community, which might benefit from current research, which includes pharmaceutical companies, patient communities and regulators of governments. First of all, our research results might provide pharmaceutical companies with preliminary data or/and ideas for their current or future product development, targeted at subjects with chronic inflammatory diseases. Secondly, patient communities could obtain important information about the cause of secondary diseases as a result of their chronic condition. A better understanding about the sources of additional health dangers that come with their medical status, may lead to behavioral changes to prevent concomitant disease, in this particular case cancer in patients with inflammatory conditions. Last, but probably the most important target group is regulators at the government. The government plays a significant role in guarding the society via promulgating regulation and law, and negotiating with industries. Specific attention can be given to setting guidelines to protect the most vulnerable populations, including diseased subjects.

1.3 Products and Innovation

For the academic community, six published scientific articles from this thesis are available online. Besides that, the results were presented at (inter)national conferences via oral presentation and poster presentations. Our studies provide leads for the effective prevention of cancer in subjects with chronic inflammatory diseases. We now
realize that every individual is different and the exposure conditions may vary for each person as well. For example, a patient may develop lung cancer due to a long-term smoking history, whereas other patients with the same type of lung cancer developed the cancer because he/ she lived in a highly polluted area with accompanying lung inflammation. Therefore, “personalized medicine” is also at place for prevention in order to further increase its effectivity. This thesis focused on several conditions that occur in subjects that are exposed to chemical carcinogens, while the lung is inflamed. Since this field has not yet been thoroughly investigated, lots remain unknown. In chapter 2, 3 and 4, we demonstrated the mechanism of how β-glucuronidase, acidic microenvironment, and IL-8 influence B[a]P metabolism and modulates the formation of DNA damage. Although inflammation is of course much more complex than these 3 factors, this simplified approach provided leads for interventions to decrease risks of cancer as secondary disease: it could be of importance to inhibit the activity and release of enzymes like β-glucuronidase or MPO, or to restore local pH to prevent increased cancer risks. Moreover, we also showed that inflammation significantly inhibited phase II detoxification processes and DNA repair. These findings offer new targets for drug development and research.

The metabolism of B[a]P in vitro is markedly different from in vivo. For instance, cytochrome P450 1A1 is an activator of B[a]P in vitro, whereas in vivo studies with CYP1A1 knockout animals indicate that CYP1A1 is an important detoxifying enzyme. The reasons for the discrepancies between in vitro and in vivo B[a]P genotoxicity remain largely unclear. However, we showed that after introducing inflammatory parameters in in vitro settings, that the metabolism of B[a]P mimicked the in vivo situation much better. Regulatory testing of chemicals relies for a large part on in vitro experiments, which are obviously not carried out under conditions that mimic the in vivo situation best. For instance, oxygen concentrations are often much higher than the levels that can be reached in vivo. Therefore, our studies give leads to further optimize the in vitro testing of chemical safety.

1.4 Future value

The current thesis can be considered as an initial search for the underlying mechanisms of the increased cancer risk in subjects with chronic inflammatory diseases. Therefore, the results of this thesis should predominantly be considered as lead-finding studies for effective intervention/ prevention in subjects with inflammatory diseases. It is important to increase the awareness of physicians and researchers for these additional risks of inflammatory diseases and that early action is needed for patients, to prevent cancer development as secondary disease. The effectiveness of combinations of treatment should therefore be investigated. The future formulation of research proposals on basis of our findings may lead to important new applications or insights for both industry and society. Although the performance of clinical trials and subsequent use of new drugs for treatment is a long process, contacts with industry may already be initiated at an early stage.
References