SYNERGY – SUMMARY APPRAISAL OF THE ACHIEVED RESULTS

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Summary

The primary focus of "SYNERGY" was to investigate the interaction of selected occupational carcinogens and tobacco smoke in the development of lung cancer. For this purpose, international population-based case-control studies were combined into one pooled data set (including approx. 18,000 lung cancer cases and 22,000 control subjects).

To estimate each participant’s life-long cumulative exposure to the selected carcinogens, a total of 100,000 personal measurements from secondary measurement databases were integrated into a job-exposure-matrix using an innovative approach. Description of dose-effect relationships and combined effects was based on the odds ratio as the relevant relative risk measure in case-control studies.

Agent-related analyses in SYNERGY so far have focused on dose-response relationships with respect to occupational exposure to asbestos. Because population-based studies include a large number of occupational activities and typical high-risk occupations are usually not included, these studies primarily produce evidence for the low-dose range of exposures, for which only a few studies with reliable risk estimates are available so far. In SYNERGY, the lung cancer risk in men exposed to 0.5 fibre-years was increased about 1.25-times compared to unexposed male subjects.

Due to the comprehensive number of cases in SYNERGY, we were able to determine the combined effect of an exposure to asbestos and smoking. We showed an over-additive effect, a result that has not yet been described in the literature in a comparably large data set. The analyses of dose-response relationships for the other carcinogenic hazardous substances in SYNERGY are still being pursued.

In addition to agent-related risks, SYNERGY also analysed lung cancer risks for selected risk occupations. Increased risks were observed for welders, miners, bricklayers and hairdressers. In addition, the risk of lung cancer was increased for occupational exposure to organic dust, diesel engine emissions and low occupational social status.

In summary, SYNERGY has developed into an important platform for occupational epidemiological lung cancer research, addressing a variety of important questions including agent-related lung cancer risks in the low-dose range and risks in relevant subgroups such as women and non-smokers.

One of SYNERGY's limitations is that the used measurement values were from secondary measurement databases and therefore not collected directly from the study participants. Thus, these measurements do not necessarily correlate with the study participants' work history with respect to location, time period, and content. This uncertainty leads to a certain degree of exposure misclassification, which may lead to biased risk estimations.

Overall, it can be stated that the epidemiological exposure and risk estimation using secondary measurement data for predominantly non-highly exposed occupations is limited due to the complexity of the exposure conditions. This complexity prevented further analyses of combined effects between the five model carcinogens in SYNERGY so far. Therefore, insights gained from SYNERGY should focus primarily on aspects of occupational prevention. Especially, questions of syncarcinogenesis derived from SYNERGY should primarily not be used in compensation law suits for occupational diseases.

Background:

When assessing the relationship between occupational exposure and disease, it is important to note that carcinogenic hazardous substances often do not occur individually but in combination with other agents (such as asbestos and polycyclic aromatic hydrocarbons (PAH), quartz and radiation, or chromium and nickel). The assessment of health risks after multiple exposures, in particular of carcinogenic substances, is therefore of great importance for occupational health prevention and for the recognition of an occupational disease. However, the evaluation of occupational combination effects of carcinogenic substances is difficult, as extensive studies and reliable exposure assessments are required to study these effects reliably.

Therefore, "SYNERGY" aimed at investigating the interaction of five model occupational carcinogens (hexavalent chromium (CrVI), nickel, PAH, quartz, and asbestos) and tobacco smoke in the development of lung cancer within the framework of population-based case-control studies. Our research approach focused on earlier studies, which were pooled into a large data set, to create a sufficiently large database to carry out statistically robust analyses of the combined effects of the five model carcinogens. International population-based case-control studies on lung cancer that collected data on lifelong occupational exposures and smoking behaviour were included. The pooled study thus provides one of the world's most comprehensive epidemiological data bases for the analysis of occupational lung cancer risks.

Material / Methods:

For the pooled analysis, original data from previous lung cancer studies were merged. Currently, sixteen case-control studies are included in SYNERGY originating from Canada (2), France (3), Germany (2), Italy (3), Sweden (1), Spain (1), the Netherlands (1), New Zealand (1), and China (1). In addition an IARC multi-centre study in Central and Eastern Europe and the United Kingdom with a total of seven centres was included. In total, nearly 18,000 lung cancer cases and 22,000 healthy control subjects were included, making it the largest epidemiological database on occupational lung cancer to date.

For SYNERGY, the large amount of measurement data in secondary databases such as MEGA at the “Institute for Occupational Safety and Health of the German Social Accident Insurance” (IFA) or COLCHIC at the “Institut National de Recherche et de Sécurité” in France were included in the exposure assessment in an innovative approach. The MEGA-database provided the largest share of measurements within SYNERGY.

A total of 356,551 exposure measurements were recorded, of which 100,000 personal measurements were used for epidemiological exposure assessment. In addition to the workplace concentrations, extensive additional information was provided, including the purpose for the measurement, the measuring device, measurement duration, and the analysis methods. A job-exposure-matrix (SYN-JEM) was constructed from these data combined with an expert-assessment of historical exposures, which quantitatively estimated mean exposure levels to the studied occupational carcinogens for each study participant and occupation using extensive statistical models, broken down by region and calendar year. In addition, accompanying technical information was taken into account. Different exposure metrics (cumulative measures, mean concentrations, and peak exposures) were considered for the study of the combined agent effects. Models also adjusted for smoking habits.

Population-based studies such as SYNERGY, unlike cohorts conducted in specific industries, offer a particular opportunity for risk assessment, as these studies can cover a wide range of occupational activities. Further advantages of SYNERGY are the uniquely large number of cases (also among women), the exposure modelling with measured data to derive agent-related risks and the possibility to adjust for smoking habits as the most important risk factor for lung cancer. The lung cancer risk for non-smokers was also determined. However, due to its design, case-control studies cannot directly deduce associated excess risks caused by exposure. SYNERGY therefore focuses on the description of dose-effect relationships and interactions are based on relative risk measures (in this case the odds ratio (OR)).

The administrative coordination of the SYNERGY study was carried out by the International Cancer Agency for Research on Cancer of the WHO (IARC), the Institute for Prevention and Occupational Medicine of the German Social Accident

Insurance, Institute of the Ruhr University Bochum (IPA) and the Institute for Risk Assessment Sciences (IRAS) in Utrecht. Further information on the SYNERGY project can be found at http://synergy.iarc.fr.

Results

Additional analyses within SYNERGY

Parallel to the main questions studied by SYNERGY, a large number of additional analyses were carried out, in particular on selected risk occupations to determine which occupations require particular prevention measures and which occupations might be considered as at risk for future compensation claims.

Which occupations are associated with an increased risk of lung cancer?

Analyses for welders, miners and bakers were carried out under the auspices of the IPA (Kendzia et al. 2014, Taeger et al. 2015, Behrens et al. 2013). For professional welders and occasional welders, the risk of lung cancer increased with increasing duration of employment. For subjects who had worked regularly as welders, we observed higher lung cancer risks compared to subjects who had welded only occasionally (Kendzia et al. 2014). The SYNERGY risk assessment with a large number of welders was considered by IARC in spring 2017 as an important result in the classification of welding fumes as a human carcinogen (group 1).

Increased lung cancer risks were also observed for miners (with more pronounced risks and trends in ore mining than coal mining, Taeger et al. 2015), bricklayers (Consonni et al. 2015), and hairdressers (Olsson et al. 2013).

For bakers (Behrens et al. 2013), cooks (Bigert et al. 2015), and firefighters (Bigert et al. 2016), no increased lung cancer risks could be observed, though.

Additional investigations

The IPA investigated in detail the influence of smoking on the distribution of histological lung cancer subtypes. It was shown that squamous cell carcinomas and small cell carcinomas are more strongly associated with smoking than adenocarcinomas (Pesch et al. 2011).

The IPA also carried out analyses of occupational social prestige and occupational social status with respect to the risk of lung cancer. Increased cancer risks for low social status (Hovanec et al. 2018) and low social prestige (Behrens et al. 2016) were observed independently of tobacco smoking and occupational exposure to known lung cancer carcinogens. Another interesting finding was that a loss of social prestige during the work life tended to be associated with an increased lung cancer risk (Behrens et al. 2016).

Furthermore, an analysis of the lung cancer risks originating from occupational exposure to organic dusts was published under the auspices of IRAS. Exposure was associated with an increased lung cancer risk and showed a dose-effect trend with increasing occupational exposure. The assumption that certain organic dusts could activate the immune system and thus protect from lung cancer could not be confirmed (Peters et al. 2012).

IARC was in charge of an analysis of lung cancer risks due to occupational exposure to diesel engine emissions (DME). For these analyses the exposure was not assessed by measurement data, but by expert semi-quantitative assessment as absent, low or high. With increasing (semi-quantitative) DME-exposure, the risk for lung cancer increased (Olsson et al. 2010).

IARC was also able to show that chronic respiratory diseases such as chronic bronchitis and emphysema are associated with an increased risk of lung cancer (Denholm et al. 2014).

Agent-related analyses in SYNERGY based on measurement data

Since cancer risk in industry-based cohorts has usually been investigated with historically high exposure levels, it is difficult to draw conclusions for the low-dose range from these studies. Scientific findings on dose-effect relationship for asbestos and lung cancer are therefore primarily available for occupations with high workplace exposure, for example in the production and processing of asbestos cement and asbestos textiles. The approach of investigating occupational risks in population-based case-control studies is of particular importance, because these studies typically lack these classical high-risk occupations and instead cover a large number of occupations with rather low occupational exposure.

So far, there are only few studies with reliable risk estimates in the low-dose range, which could be evaluated in detail within the framework of SYNERGY. The lung cancer risk in SYNERGY was 1.25 times higher in men exposed to 0.5 fibre-years of asbestos. The highest exposure category for asbestos in SYNERGY was >2.8 fibre-years, which was associated with an OR of 1.38 (95% CI 1.27-1.50).

Combination effects with smoking

Based on the large number of cases in SYNERGY, we tried to calculate the combined effect of asbestos and smoking. So far, we were able to analyse the combined effects on lung cancer risk for men who had smoked (yes/no) in combination with an exposure to asbestos (ever/never). An OR of 1.26 (95% CI 1.04-1.53) was observed for asbestos exposure among never-smokers. Male smokers without exposure to asbestos showed OR=9.23 (95% CI 8.13-10.5), which increased to OR=11.9 (95% CI 10.5-13.3) in the case of the combined exposure (ever smoking and ever asbestos).

The combined effect of asbestos and tobacco smoking thus showed an over-additive effect (Olsson et al. 2017). This result has not yet been described in the literature in a comparably large data set and is also plausible from a mechanistic point of view.

Limitations in the analysis of agent-related risks in SYNERGY

A fundamental difficulty is that, due to the strong influence of smoking, it is difficult to reliably determine the (comparatively lower) cancer risk for another carcinogenic substance. Heavy smokers have a 100-fold increased risk of developing squamous cell or small cell lung cancer (Pesch et al. 2012). In general, many occupationally exposed workers also had smoked in the past, which poses the danger that agent-related risks are suppressed by the dominant influence of smoking. SYNERGY with a relevant number of non- and low-dose smokers enabled a subgroup analysis in order to determine lung cancer risk from exposure to occupational carcinogens. We showed that male non-smokers with an asbestos exposure of more than 1.2 fibre-years had an OR of 1.51 (95% CI 1.16-1.97) compared to non-smokers without asbestos exposure.

In general, estimation of exposure in epidemiological studies is associated with uncertainty, which can lead to bias in the risk estimation. Measurements from secondary measurement databases (i.e. measurements on persons other than the study participants) and databases of individual countries (such as MEGA or COLCHIC) were also used in SYNERGY to estimate the typical mean exposure of study participants from other countries. In addition, there was a lack of personal measurement data for past work periods, i.e. for other periods of time than covered by most study participants' work histories. Moreover, many measurements did not reach the analytical detection limit and had to be statistically replaced ("imputed") by an estimated value.

Another possible source for exposure misclassification are the measured values themselves. In contrast to specific industrial cohorts, classical high-risk occupations rarely occur in population-based studies, e.g. workers in asbestos cement production (Peters et al. 2016). However, most secondary asbestos measurements in SYNERGY originated from these high-risk occupations. In order to expand the measurement data base, these as well as measurement values in occupations that are usually not exposed were also used for the exposure assessment.

The strength of a possible bias due to exposure misclassification depends on the risk factor prevalence (the rarer, the stronger) and on the specificity of exposure assessment (bias increases with decreasing specificity). This means that misclassification of non-exposed subjects as exposed usually produces a stronger bias than misclassification of exposed persons as non-exposed. In SYNERGY a high exposure sensitivity was pursued, which rather leads to high exposure prevalence estimates (e.g. 40% of men ever exposed to asbestos) (Olsson et al. 2017).

In addition, certain activities such as welding may be misclassified if the welding process cannot be correctly identified. Misclassification may occur, e.g. when estimating exposure to Cr(VI) and nickel. Depending on the welding process, exposures may differ by a factor of more than 100 (e.g., Cr(VI) 0.05 µg/m^3 for laser welding and 7.9 µg/m^3 for manual arc welding, Pesch et al. 2015). A more accurate exposure assessment for welders, however, requires the analysis of job-specific questionnaires (JSQ), which solicit more detailed information on the welding procedure. Such JSQ were only solicited in a few SYNERGY sub-studies.

IPA evaluated welding-related JSQ from two German sub-studies with additional information on the welding process in a separate analysis and developed a Welding-Exposure-Matrix (WEM) based on measurement values from MEGA. The WEM thus provides more precise information on welders' agent-related exposure to welding fumes, Cr(VI) and nickel depending on the applied welding process than the SYN-JEM. IPA summarized results from these analyses in a manuscript which will be published in due time. The distinction of cancer risks to individual substances in welding fume, however, proved to be difficult because total chromium or Cr(VI) and nickel may highly correlate in welding fumes (Weiss et al. 2013).

Conclusions

SYNERGY has developed into an important platform for occupational lung cancer research. The size of the database allows the estimation of occupational and agent-related risks and the analysis of cancer risks in relevant subgroups such as women and non-smokers.

In addition to asbestos, dose-response relationships for the other carcinogens that are the focus of the SYNERGY project are currently being pursued. However, the risk estimates achieved to date for the selected substances already provide important findings for the low-dose range and the interaction with smoking habits.

Overall, however, it can be stated that the epidemiological exposure and risk estimation of predominantly non-exposed occupations by means of secondary measurement data, as available in SYNERGY, reaches its limits due to the complexity of the exposure conditions. This complexity has also led to the fact that no further interactions between the five model carcinogens in SYNERGY (Cr(VI), nickel, asbestos, PAH and quartz) could have been derived yet.

In regulation, there is an increasing discussion as to how the interaction of several carcinogens in the assessment of occupational diseases should be evaluated if no concrete numbers on the combined effects of individual hazardous substances are available. We argued in a recent publication (Behrens et al. 2018a) that simplifying assumptions, e.g. in the sense of a simple addition of individual risks, cannot do justice to the complex exposure circumstances in companies or the complex mechanisms involved in (cancer) development. These assumptions may possibly be used for prevention purposes, but simple addition of two associated risks should not be regarded as a "gold standard" for carcinogenesis. Here, a multitude of molecular, genetic, occupational and non-occupational exposures or risk factors may lead to cancer, in which additive synergistic effects of two substances may be causal in only a few cases. Considering possible combination effects in the absence of concrete epidemiological data, we therefore proposed to allow a more qualitative evaluation synergistic effects in regulation, provided that there is scientific evidence for a cumulative effect. The precise prerequisites and necessary evidence for such an opening clause on syncarcinogenesis still need to be defined in a dialogue between physicians, natural scientists, and lawyers, though. Due to the circumstances described above, results from SYNERGY (in particular on questions of syncarcinogenesis should not be used for questions on compensation for occupational diseases yet. SYNERGY findings should primarily focus on aspects of occupational prevention (Behrens et al. 2018b).

Nevertheless, SYNERGY offers a platform for carrying out further analyses that can provide important insights into future questions of occupational medical prevention. These include, for example, the investigation of time patterns of exposure to several carcinogens (parallel or delayed), an in-depth exploration of the measurement data obtained with different methods, alternative assumptions to historical exposure, and the application of further statistical methods for the treatment of measurement data below the detection limit.

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