UNIKLINIK RWTH AACHEN

FAQ / report for submission

to the Ministry of Culture and Science of the State of North Rhine-Westphalia

on the NO_2 study by the Institute for Occupational, Social and Environmental Medicine of Uniklinik RWTH Aachen

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Introduction

In the spirit of freedom of research and teaching, this list of questions is intended to comprehensively present the facts surrounding the “NO2 study” on the occasion of the handover of the report to the Ministry of Culture and Science of the State of North Rhine-Westphalia. The scientific tasks of occupational medicine include experimental studies into the effects of substances found in the workplace under strictly controlled conditions, so that harmful effects in the workplace can be prevented. It is right and important that there are such studies. They benefit entire professional groups. However, the extent to which study results are used for interpretations, possibly even improperly in terms of a scientifically incorrect classification, is beyond the reach of any scientist.

Aachen, 2nd February, 2018

Questions regarding the EUGT

Did RWTH approach the EUGT or vice versa?

The study was devised in Munich by Rudolf Jörres (co-author of the study) in 2010/2011, which was before the Institute for Occupational, Social and Environmental Medicine of Uniklinik RWTH Aachen (hereinafter referred to as “Institute”) became involved. The original plan was also for the study to be implemented in Munich, this was however not possible for technical and time reasons. That is why the Institute for Occupational, Social and Environmental Medicine became involved in 2012. At that time, the EUGT was already known as a potential sponsor of the study. The research proposal was updated, developed further and then submitted to the EUGT. The study design, including methodological aspects, was devised completely independently of the EUGT.

What did the head of the study and his team know about the aims and motives of the EUGT?

It was known that the EUGT e.V. is funded by the automotive industry. There are four conditions at the Aachen-based Institute that must all be met before industry funding can be accepted:

- No influence on the study design
- No influence on the study execution
- Free publication rights
- Transparency of funding

All conditions were met in full, so we accepted the funding opportunity.

Was it contract research?

It was contract research in the sense that the research sponsor commissioned the Institute to conduct the study after submitting the research proposal. But the goal of the research contract was not specified by the client/sponsor and the research results as well as the publication, intellectual property, usage and exploitation rights and copyrights were not reserved to the client. All of the above four conditions applied (no influence on the study design, no influence on the execution of the study, free publication rights, transparency of funding).

If there is no link to diesel, why did the EUGT fund the study?

For one, the study was primarily about the issue of occupational exposure limits (there is a lot of welding in the automotive industry, which also means NO2 exposure in the workplace) and secondly, there was also certainly interest in whether there are any effects at environmentally relevant concentrations, which the Institute with its extremely sensitive methodology may have been able to determine. For a precise answer, the EUGT should be asked this question.

What was the research interest of the study? Is not there a conflict of interests because the client was also the beneficiary of the study?

This would be relevant if the “client” was to influence the conception and execution and/or publication should only happen if the results are as “desired”. That was definitely not the case (see also the question: Was it contract research?).

Were there even any significant results to be expected, considering the short exposure time of just three hours? Or was the study mainly intended to serve a specific interest group?

On the basis of older literature studies with less sensitive methods, the team led by Prof. Thomas Kraus had expected that effects would be visible at least at the highest concentration, possibly even at the current MAK value (MAK = *Maximale Arbeitsplatzkonzentration*, maximum permissible concentration at the workplace). From other exposure scenarios it is known (for example in ozone) that subclinical inflammatory reactions can already occur within the first three hours. The study design was insofar scientifically well-founded.

Did the staff members of the Institute have contact with EUGT staff during the study that may have been able to influence them?

There was occasional telephone contact to ask when we would be finished, as we had a preparatory phase of several months beforehand (investigations in early 2014).

What did the EUGT pay for the study at Uniklinik RWTH Aachen? The media reports around 75,000 euros.

It is unknown how this figure in the media came about. It is wrong. Such a complex study would not have been feasible for that sum. The third-party funding agreement with Uniklinik RWTH Aachen amounted to 220,000 euros.

Were there any other EUGT-funded studies?

At the Institute there was a literature paper in 2013 on the topic: „Literatur und aktuelle Datenlage zur elektromagnetischen Interferenz elektronischer Implantate im kHz-Bereich“.

Questions about the study/course of the study in particular and in general

Who submitted the research application for the study?

Initially the Institute for Occupational, Social and Environmental Medicine of the LMU Munich, in 2012 the Institute for Occupational, Social and Environmental Medicine of Uniklinik RWTH Aachen together with the LMU Munich.

When was the study conducted, when was it published?

The study preparations took place in 2013. The study was conducted in January/February 2014. The publication was published in 2016.

What was the purpose of this study? After all there was already a limit, and the DFG derives that from study results? What was different about the NO2 study?

The DFG pointed out in the MAK-explanation that the available recent studies did not allow valid statements on the sole effect of NO2. Some older studies used conventional methods to detect effects. For the first time, the research team used extremely sensitive methods in such a study that can detect an effect long before conventional methods, such as lung function, show any impact. For that reason, the research team also expected to detect effects with the methodology.

What did it all achieve? The limit remains unchanged?

The results support the derivation of the new limit and indicate that short-term exceedance during a single shift (MAK value is an 8-hour average) is not associated with any effects. A MAK value is not legally binding. Under inclusion of the NO2 study published that year, the new occupational exposure limit of 0.5ppm was incorporated into the TRGS 900 (TRGS = *Technische Regeln für Gefahrstoffe*, Technical Rules for Hazardous Substances) in 2016, making it legally binding.

How many subjects participated in the study and according to which criteria were they selected?

There were 25 participants. They were admitted if they met the inclusion criteria defined in the study protocol (age of majority, non-smokers, no heart or lung disease, no infections, no participation in other studies, written informed consent).

How often and for how long were the subjects exposed to NO2? What did the subjects do during this period? Were there 25 people in a single room?

Each subject was exposed once per week for three hours for four consecutive weeks. There were five subjects together in the exposure laboratory. The subjects were allowed to occupy themselves freely: reading or studying, some groups also played board games.

What physiological reactions were measured?

A variety of medical parameters were recorded before and after exposure, e.g. lung function, using a variety of extremely sensitive procedures. However, the researchers looked in particular for immune system markers that could give an indication of an early immune response. These markers were looked for in the blood, nasal secretions, sputum and exhaled air. No statistically significant health effects were detected in the course of this..

How much were the subjects paid? Were the subjects comprehensively informed?

The subjects received an allowance of 100 euros per day. All subjects received the written participant information in advance to prepare for an informed consent meeting. The informed consent meeting took place some time before the start of the study and was conducted by the responsible physician. Thereafter, the subject could give his written consent.

How are the subjects today? Have there been any checks to find out whether any of them suffered health damage after all?

The subjects were informed in writing in the participant information that they would have to notify the study physician immediately of any adverse health effects that might be related to the study. In such an event, the Ethics Committee would have become involved immediately. There has been no notification of that kind, neither during the course of the study, nor after.

Why did the study have to be performed on humans? Was there no alternative to this study (or in general)?

Studies conducted on animals or cell systems are very difficult to use for determining and reviewing exposure limits in occupational medicine. This is due to the fact that humans and animals often differ significantly. Animal experiments can be used to indicate mechanisms that may play a role. Investigations with humans are a piece of the jigsaw and can be used for derivation.

Why were the subjects exposed to substances known to be harmful to health?

Whether a substance is harmful to health is crucially dependent on the dosage (and the exposure time). In this study, NO2 concentrations were used with which health damage at short-term exposure could be excluded with absolute certainty. The aim of the study was to identify early reactions of the immune system that, although fully reversible after short-term exposure, may cause long-term adverse effects at chronic or repeated exposure.

How often are there studies with test subjects? Please provide examples of such studies.

Occupational health studies are usually carried out using test subjects, as the research is very application-oriented. This may for instance be done directly in the workplace. The disadvantage with this is often that influencing factors are difficult to control. For that reason, studies are conducted in strictly controlled experimental settings.

Additionally, the Institute is researching the long-term consequences of exposures that occurred in the workplace decades ago. The focus here is for instance on improving the early detection of asbestos-related diseases. For this purpose, the Institute conducts a prospective cohort study with approximately 8,600 subjects who are regularly offered medical screening and whose results are then scientifically evaluated. A further cohort of 300 people who were exposed to extremely high concentrations of PCBs in the workplace are also being scientifically analysed.

How many funded studies is the Institute currently conducting?

The Institute is currently conducting 15 studies.

Questions about the Ethics Committee

Who belongs to the Ethics Committee at the Faculty of Medicine of RWTH Aachen?

The Ethics Committee at the Faculty of Medicine of RWTH Aachen is an independent body with eight voting members. Four members are physicians who are also assistant professors, the other four members are non-physicians, one member is a lawyer with the qualifications to become a judge, one member has professional experience in the field of ethics, one member is a patient representative (lay representative), one member is a pharmacist (for the evaluation of applications under German drug and medical product laws). This corresponds to the required composition for an Ethics Committee constituted under state law (see Healthcare Profession Act NRW).

How are the members of the Ethics Committee appointed?

The proposal for new, qualified members usually comes from within the ranks of the incumbent Ethics Committee itself. The members, who are proposed for a term of four years, are confirmed by the faculty council, which also elects the chairperson. The vice-chairperson is elected by the Ethics Committee from among its members.

What are the tasks of an Ethics Committee?

The medical Ethics Committee has the task of ethically and legally assessing research projects using human test subjects that are to be conducted at the Faculty of Medicine of RWTH Aachen or at one of its institutions and to advise the responsible researchers.

Consultation by the Ethics Committee also takes place when research is planned on deceased subjects, removed bodily samples or epidemiological research with personal data.

The Ethics Committee assesses whether the research project can be approved from an ethical and legal point of view. Studies on humans using somatic cell therapy, gene transfer and genetically modified organisms are also assessed by the Ethics Committee.

Which studies must be assessed and approved by the Ethics Committee?

In accordance with the medical professional code of conduct, all physicians must consult an Ethics Committee on the ethical and professional issues associated with their project before carrying out studies on humans. The Ethics Committee does not issue an approval, but evaluates favourably (in some federal states, studies outside of German drug and medical product laws are based solely on consultation, without a check of the final documents). For studies under German drug and medical product laws, there is also a legal obligation for the responsible Ethics Committee and the competent higher federal authority (Federal Institute for Drugs and Medical Devices or Paul Ehrlich Institute) to evaluate the ethical and legal aspects of the study.

According to what criteria does the Ethics Committee assess whether a study may be conducted?

The Ethics Committee performs its assessment in accordance with recognised, current, scientific procedures and criteria as well as relevant national and international ethical norms and standards. These include, for example, the

- De Declaration of the World Medical Association of Helsinki on medical research involving human subjects in its current version
- Professional Code of Conduct of the Ärztekammer Nordrhein
- Heilberufsgesetz (HeilBerG) [Health Profession Act]
- Gesetz zum Schutz personenbezogener Daten im Gesundheitswesen (Gesundheitsdatenschutzgesetz - GDSG NRW) [Law for the Protection of Personal Data in Health Care]
- Arzneimittelgesetz (AMG) [Drug Law]
- Medizinproduktegesetz (MPG) einschließlich Verordnung über klinische Prüfungen von Medizinprodukten (MPKPV) [Medical Devices Act incl. Ordinance on Clinical Trials with Medical Devices]
- Gesetz zur Regelung des Transfusionswesens [Law Regulating Transfusions]
- Strahlenschutzverordnung (StrlSchV) [Radiation Protection Ordinance]
- Röntgenverordnung (RöV) [X-ray Ordinance]
- Verordnung über die Anwendung der Guten Klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung am Menschen (GCP-Verordnung – GCP-V) [Ordinance on the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use]

In addition to the observance of valid ethical norms and standards and the legal requirements, a benefit-risk assessment is a fundamental part of every consultation process. There is a general distinction between own and group benefits. In any case, the benefits must be greater than the potential risks. Special attention is also paid to the written information provided to the subject or patient: the subject/patient must be fully informed about the course of the study and possible risks so that he or she can decide to participate in the study or not (informed consent). The consent is given by signing the declaration of consent, however, the subject/patient can revoke his consent at any time without giving reasons and without personal disadvantages.

How many cases does the Ethics Committee handle? Which cases have been rejected?

In 2017, 169 studies were processed by the full Ethics Committee. Practically all submitted studies receive suggestions for improvement or refusals in subsection. After the applications have been revised, there is either an affirmative assessment or yet more additional contentual requirements are lodged. Some applicants then decide to not revise their applications, which amounts to rejection. This probably affects five to ten percent of the studies.

When was the application for the NO2 study submitted to the Committee and when was it decided? Is this done with a voting procedure? If so, how exactly?

The application for the study was received by the administrative office on 20/02/2013. On the same day, the study materials were electronically provided to members of the Ethics Committee for evaluation; there were also formal additional requirements. The consultation took place by way of electronic circulation, all comments were made in writing and were available to all members. The study was approved by all members after intensive consideration of the matter. The additional requirements were sent to the applicants on 07/03/2013. A revised application was submitted on 19/03/2013, which met the additional requirements. On 28/03/2013, a positive vote was sent with the requirement to submit the insurance policy.

Did anyone have any concerns or was the research proposal unanimously approved?

There were never any concerns about the submitted research proposal because there was no evidence of any risk. The Committee asked questions and provided guidance, as is also standard in every other study. The research proposal was approved unanimously.

How does the Committee ensure that clients funding academic studies pursue “sound” purposes from a scientific-ethical perspective??

One of the aspects included in the consultation process as standard are the test schedules, which must state the background and purpose of the study as well as the scientific enquiries and the study objectives. These documents are subject to an ethical review and are the basis of the decision. Against the background of a recognisable personal benefit of patients or a group benefit, a commercial interest of sponsors in the study results should not be regarded by default as reprehensible. An unethical enquiry is unacceptable in any case. In general, the Ethics Committee urges that the data collected should be published.