Factsheet

DANGEROUS CONFIDENCE IN "GOOD LABORATORY PRACTICE"

1. Introduction

Our authorisation system for chemicals is based on the principle that manufacturers must prove, by means of scientific studies, that their products do not pose unacceptable risks to public health and the environment. It is therefore also the responsibility of manufacturers to commission certified contract laboratories to carry out the toxicological studies necessary for the approval procedure. As a guarantee against manipulation and falsification of these "regulatory" studies, regulatory authorities worldwide rely on the certified standard of "Good Laboratory Practice" (GLP). This standard provides for strict documentation requirements and regular internal and external controls. However, the current fraud scandal involving a German contract laboratory certified according to GLP, shows that this trust is unlikely to be justified. According to reports, GLP studies have been manipulated and falsified there since 2005.

In October 2019, the investigative ARD news magazine FAKT shocked Germany with serious fraud allegations against one of the largest German animal testing laboratories, the Laboratory of Pharmacology and Toxicology (LPT) Hamburg. This company is a contract laboratory which carries out regulatory studies on behalf of the pharmaceutical and chemical industry. Until now, the authorities considered studies carried out under GLP to be reliable and forgery-proof. GLP is a legally binding standard for regulatory studies, which was introduced in the late 1970s to prevent scientific fraud.

The current case came into play after an animal welfare activist who had infiltrated one of the three LPT branches, reported serious manipulation of a drug study. After broadcasting a TV report on the subject, several former employees came forward and described similar breaches, which date back to 2005.

Recent research now shows that LPT has also produced studies that were part of the study package for the EU-wide approval of glyphosate in December 2017: One in seven studies in this package, which was the basis to grant re-approval for glyphosate, came from LPT. These findings are worrying in two ways:

- On the one hand, there is the fundamental question of whether the risk assessments for medicines, pesticides and chemicals based on LPT studies can be trusted.
- Even more worrying is the general realisation that laboratories, despite the supposedly "tamper-proof" GLP standard, are apparently able to falsify studies over years and decades without being noticed by the control authorities.

The classification of glyphosate as "non-carcinogenic" and "not genotoxic“ is based, among other things, on the European authorities' full confidence in the GLP system. In the EU assessment proces GLP studies were automatically classified as reliable; This in stark contrast with the numerous "non-GLP studies" from university research, peer reviewed and published, most of which reported evidence of a genotoxic effect and an increased risk of lymphatic cancer in users of glyphosate, were disqualified by the authorities as „unreliable“.

The LPT counterfeiting scandal reveals the failure of a regulatory system, that places the commissioning and preparation of studies in the hands of industry. At the same time, it confirms the urgency of a fundamental reform of this system for identifying the risks of chemicals, as called for by the European coalition "Citizens for Science in Pesticide Regulation" in October 2018.[1]

2. Background

2.1. Manipulation and falsification of GLP studies at LPT Hamburg

With around 175 employees, LPT Hamburg is one of the largest contract laboratories in Germany, which prepares regulatory studies according to GLP on behalf of the pharmaceutical and pesticide industry. It has three locations: Mienenbüttel in Lower Saxony, Neugraben in Hamburg and Wankendorf in Schleswig-Holstein.

From December 2018 to March 2019, "Soko Tierschutz" brought in an undercover investigator at the Mienenbüttel site. This investigator documented violations of animal protection regulations as well as the case of a monkey that died in the course of a drug study and whose death was covered up.

After the ARD news magazine FAKT had reported this suspected case of serious scientific fraud in its broadcast of 15 October 2019[2], several former employees contacted the FAKT editorial office and described similar cases of fraud that were taken up by FAKT in the broadcasts of 5 November 2019[3] and the broadcast of 26 November 2019[4].

The following will summarise the five cases presented by the FAKT programme, which indicate repeated and systematic manipulation and falsification of studies in the period between 2005 and 2019:

Case 1: Exchange of dead monkey for living animal (2018 - 2019)

This case is based on the report of the infiltrated animal protectionist (quote from broadcast of 15.10.2019):

> *The animal rights activist infiltrated a monkey study for a South Korean pharmaceutical company The story is about a monkey, which is documented as test-animal with the number "31 m". His tattooed number, according to documents, is 1601371. But the monkey from this cage has a completely different number tattooed on it according to the undercover investigator.*

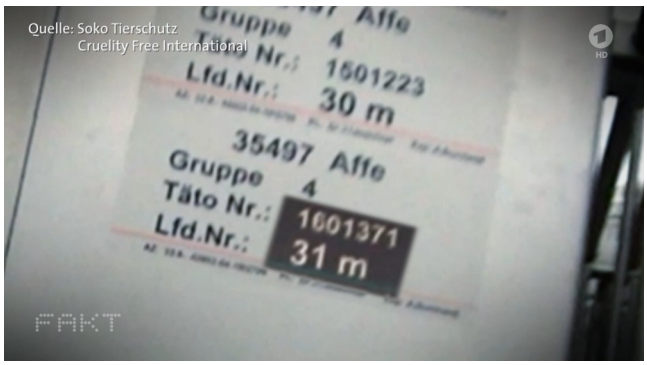

Fig.1: Cage label of the deceased '31 m'

We meet the man who was „planted“. He'd have been told the following story by his colleagues:

"The real 31m died after 6 weeks of an intestinal prolapse and was replaced by another monkey a year older."

The employees make no secret of this when talking to each other. Excerpts from the memory protocol of the infiltrated animal protectionist:

"The wrong 31m is here" - "Exactly, the replaced one" - "You're a very wrong guy" - "Since October, yes, it's a hammer" - "But he's settled in well here. The tatoo numbers are exchanged at the section - just put the other one in, that's how it works here".

Four further conversations are documented by the infiltrated animal welfare activist, who also confirm this monkey exchange. In the documents however nothing of it is found back. The original tatoo number is used unchanged from the beginning to the end of the experiment. Such an exchange should have been reported to the authorities and approved by them. We inquire at the responsible Lower Saxony State Office for Consumer Protection and Food Safety and receive the following answer: Neither the death of an animal nor the exchange was reported to the office by the company. (End of quote)

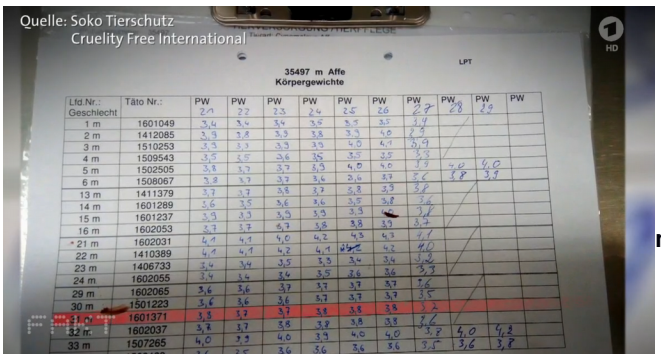

Fig.2: The tattoo number of the deceased '31m' is used until the end of the experiment (red marking)

Case 2: Exchange of dead rats

In the programme of 5.11.2019 a former employee reports about a short-term study with rats at the LPT-Wankendorf site in Schleswig-Holstein. The animals had been administered a test substance in three different dose groups. Animals died only a few days after the start of the trial. But instead of documenting this result according to the regulations, the deceased animals were replaced by new ones. According to media reports, the public prosecutor's office in Kiel is now investigating this case on suspicion of manipulation of study results.[5]

Case 3: Regular and systematic falsification of study protocols

Another former LPT-employee testifies in the broadcast of 5.11.2019 that she witnessed forgeries at the Hamburg site and also forged data herself on instructions (quote from broadcast):

> *"I not only experienced it, I did it myself. I forged documents; our studies. If the results did not meet expectations, I was asked to improve them. The data that did not fit in were marked so that I could enter the data on the blank protocol the new values that were given to me. The new report was also marked with the old date and my signature..." Later on, she had refused to make such forgeries. Subsequently, other employees took over this task.“*

Later she refused to make such forgeries and other employees took over this task, according to the witness.

Case 4: Exchange of dead monkey for living animal (2005)

In the programme of 26.11.2019, a former employee, who was employed at the LPT from 2003 to 2005 and was head of haematology for all three locations, reports on the replacement of a deceased monkey in a cancer study in which a cytostatic drug was tested (quote from broadcast):

> *"These animals, especially in the high-dose group, actually had completely open skin - so it was the raw meat that was visible, miserable really miserable. [...] In fact, one animal died in the high-dose group and was replaced by another animal. Here, too, the tattoo number, which is in the chest area of the animal, was cut out of the dead animal and added to the organs of the replaced animal after the end of the study. So that it looks as if this animal had not died at all.“*

Case 5: Falsification of tumor findings

The fifth witness was employed as a research assistant at LPT Hamburg for one year from 2004. During this time he had written studies in which he noticed that results had been falsified. For example, "tumours detected in the test, then turned into inflammations in the study" (i.e. in the study report). After he left the company in mid-2005, he informed the competent authority of his observations. However, he had never heard anything from the responsible authority again (quote from broadcast):

"So, a few months after I left LPT, I contacted the responsible authorities here. And had an appointment. And in this appointment we discussed the LPT issue together. It was also about manipulation of data and of course it was also about the fact that studies were so strongly influenced that it was not compatible with my conscience."

When asked by FAKT, the competent authority for health and consumer protection stated, that "the active employees were not aware of any indications of forgeries from the period in question". There was also nothing in the files, as the authority only kept documents for ten years.

2.2 LPT studies in the glyphosate approval process

An electronic screening of the glyphosate assessment report[6] showed that approximately one in seven of the 150 "new GLP studies"[7] submitted as part of the approval procedure could be attributed to LPT Hamburg. As shown in the table below (Fig. 3), fourteen studies have the abbreviation LPT in their report number (number code). As the facsimile from the evaluation report (Fig. 4) shows, this code clearly indicates that the study was assigned to the "*LPT Laboratory of Pharmacology and Toxicology GmbH & Co. KG, Hamburg, Germany*". Seven further studies (number code marked in red) can also be assigned to the LPT due to the fact that they were prepared by the same study authors in the same implementation period 2009 – 2010.

For numerous other studies, no clear assignment to a test laboratory was possible due to blackenings in the assessment report. In total, 21 or more of the 150 new GLP studies submitted by Monsanto in May 2012 for glyphosate re-approval are likely to have come from LPT laboratories.

Year	Autor	Number Code	Study title	ASB-Code (reliable searchterm)	Page Seite RAR-Addendum
2009	Leuschner	LPT 23913	Acute Dermal Irritation/Corrosion Test (Patch Test) of Glyphosate TC in Rabbits	ASB2012-11421	665, 1435
2010	Leuschner	LPT 24605	Acute Dermal Irritation/Corrosion Test (Patch Test) of Glyphosate TC in Rabbits	ASB2012-11422	667, 1435
2009	Leuschner	LPT 23914	Acute Eye Irritation/Corrosion Test of Glyphosate TC in Rabbits	ASB2012-11432	53, 55, 697, 1438
2010	Leuschner	LPT 24606	Acute Eye Irritation/Corrosion Test of Glyphosate TC in Rabbits	ASB2012-11433	53, 55, 700, 1438
2009	Haferkorn J	LPT 23912	Acute Dermal Toxicity Study of Glyphosate TC in CD Rats	ASB2012-11398	605, 1430
2010	Haferkorn J	LPT 24876	Acute Dermal Toxicity Study of Glyphosate TC in CD Rats	ASB2012-11399	607, 1431
2010	Haferkorn J	LPT 24604	Acute Dermal Toxicity Study of Glyphosate TC in CD Rats	ASB2012-11400	609, 1431
2009	Haferkorn J	LPT 23911	Acute Inhalation Toxicity Study of Glyphosate TC in Rats	ASB2012-11409	631, 1433
2010	Haferkorn J	LPT 24875	Acute Inhalation Toxicity Study of Glyphosate TC in Rats	ASB2012-11410	1433
2009	Haferkorn J	LPT 23915	Examination of Glyphosate TC in Skin Sensitisation Test in Guinea Pigs according to Magnusson and Kligman (Maximisation Test)	ASB2012-11443	727, 1440
2010	Haferkorn J	LPT 24607	Examination of Glyphosate TC in Skin Sensitisation Test in Guinea Pigs according to Magnusson and Kligman (Maximisation Test)	ASB2012-11444	729, 1440
2009	Flügge C	LPT 23916	Mutagenicity study of glyphosate TC in the salmonella typhimurium reverse mutation assay (in vitro)	ASB2012-11468	832, 1445
2010	Flügge C	LPT 24880	Mutagenicity study of Glyphosate TC in the salmonella typhimurium reverse mutation assay (in vitro)	ASB2012-11469	834, 1445
2009	Flügge C	LPT 23917	Micronucleus Test of Glyphosate TC in Bone Marrow Cells of the CD Rat by oral administration	ASB2012- 11479	65, 871, 4214
2009	Leuschner	24877	Acute Dermal Irritation/Corrosion Test (Patch Test) of Glyphosate TC In Rabbits	ASB2012-11419	662, 1435
2009	Leuschner	24878	Acute Eye Irritation/Corrosion Test Of Glyphosate TC In Rabbits	ASB2012-11429	690, 1438
2010	Haferkorn J	24874	Acute oral toxicity study of Glyphosate TC in rats	ASB2012-11386	572, 1427, 3554
2010	Haferkorn J	24602	Acute oral toxicity study of Glyphosate TC in rats	ASB2012-11387	573, 1427, 3543, 3554
2010	Haferkorn J	24603	Acute Inhalation Toxicity Study of Glyphosate TC In Rats	ASB2012-11406	624, 1433
2010	Haferkorn J	24879	Examination Of Glyphosate TC In The Skin Sensitisation Test In Guinea Pigs According To Magnusson And Kligman (Maximisation Test)	ASB2012-11440	721, 1440
2009	Haferkorn J	23910	Acute oral toxicity study of Glyphosate TC in rats	ASB2012-11385	3543,3554

Fig.3: Tabular overview of 21 studies whose origin at the Laboratories for Pharmacology and Toxicology (LPT) can be clearly traced in the assessment report on glyphosate

7th new Ames test (Flügge, 2009)

Reference: IIA, 5.4.1/07

Report: Flügge, C. 2009 Mutagenicity study of Glyphosate TC in the *Salmonella typhimurium* Reverse Mutation Assay (*in vitro*)
LPT Laboratory of Pharmacology and Toxicology GmbH & Co. KG, Hamburg, Germany
Data owner: HAG
Report No.: LPT 23916
Date: 2009-04-30
Unpublished, ASB2012-11468

Guidelines: OECD 471

Deviations: None

GLP: Yes

Acceptability: See RMS comment

Fig.4: Facsimile from the chapter on Genotoxicity in the EU assessment report of glyphosate[8]

2.3 Glyphosate and confidence in GLP

On the issue of genotoxicity of glyphosate, the EU authorities' assessment report[9] lists a total of 46 GLP studies, either conducted by the manufacturers themselves or by their contracted laboratories, three of which were conducted by LPT.

In addition to these 46 GLP studies, the regulatory authorities were required by law[10] to include all relevant independent studies from the scientific literature in their assessment. As can be seen from the evaluation report, 72 studies or tests, most of which were carried out at university or state research institutions, were available for this purpose. (3)

As shown in the following figure (Fig. 4), the GLP studies of the manufacturers report, with one exception, showed that glyphosate or glyphosate-containing pesticides do not cause genotoxicity, while the vast majority of the independent studies showed the opposite:

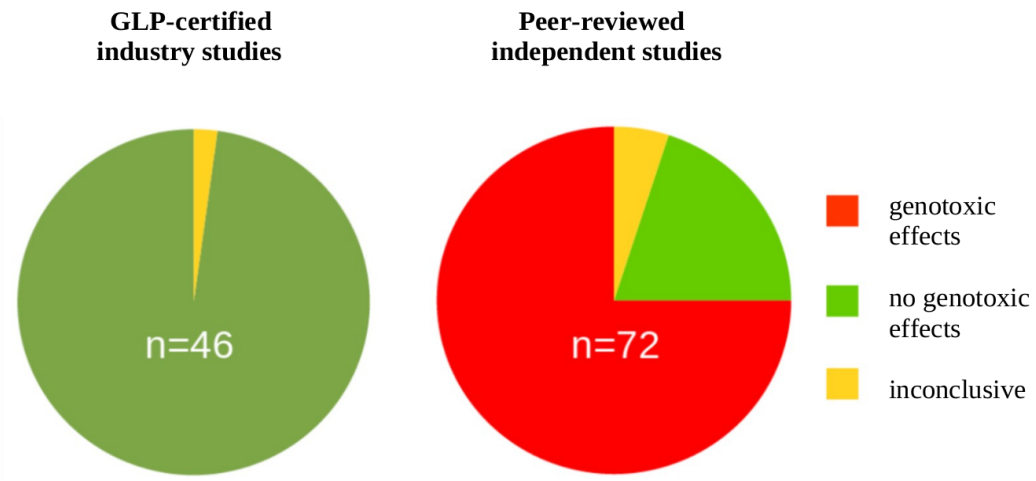

Fig.5: Diverging results on the genotoxicity of glyphosate in GLP-certified industrial studies (Left side: green = "not genotoxic") and peer-reviewed published studies (Right side: red = genotoxic"), yellow = inconclusive.

The different assessments of genotoxicity (a recognised mechanism for the development of a cancer) was an important part of the controversy surrounding the cancer assessment of glyphosate. The approach of the authorities was in general that GLP studies were automatically labelled "reliable", while university, peer reviewed studies were considered "not reliable" or "reliable with restrictions" due to the missing GLP-status: This approach created an imbalance with significant implications for the outcome of the assessment.

Unlike the experts from the International Agency for Research on Cancer (IARC) of the WHO, who recognised the "strong evidence" for the genotoxicity of glyphosate in the published studies[11], the EU authorities relied unilaterally on the GLP studies of the manufacturers, which they classified as reliable. As a result, they stated that glyphosate is "non-genotoxic" and, therefore, there is no molecular mechanism to explain its carcinogenicity.

How little justification there really is for this trust in the GLP standard as a guarantee for the reliability and counterfeit-proofing of industrial studies, was now brought to light in a shocking way by the current fraud scandal at LPT laboratories.

2.4 GLP - a supposedly forgery-proof standard

Approval procedures for pesticide active substances worldwide are based on the principle that applicants carry out the necessary studies themselves or act as study owners if they commission these studies at a contract laboratory.

The results of these studies determine whether and under what conditions an active ingredient may be marketed. It is therefore clear that the studies are of great economic importance. This also means that this procedure is objectively burdened with a conflict of interest. The gigantic “IBT-scandal” (IBT = Industrial Bio-Test Laboratories) was a striking proof of this conflict when in the 1970s, IBT, the largest private research laboratory at that time, manipulated and falsified studies for more than a decade, for example by replacing deceased animals without documenting it, and systematically falsifying experimental data[12, 13].

In response to this fraud scandal, the then new quality assurance system GLP was introduced in the USA in 1978. GLP provides a legal framework for planning, conducting and monitoring regulatory studies. The manipulation and falsification of data should be prevented with the mandatory daily documentation of all activities and observations and with the archiving of protocols, findings and tissues from animal experiments.

In 1992, the Organisation for Economic Cooperation and Development (OECD) adopted „the 10 principles of GLP“, making the system a worldwide standard. Following the OECD, the EU adopted these GLP-principles in Annex 1 of Directive 2004/10/EC.

In the EU it is up to the Member States to monitor the integrity of the GLP system by means of regular and thorough GLP inspections. Thus, the GLP inspection services of the Member States have the obligation to inspect each test laboratory at least every 2 years, i.e. to carry

out a full audit of the test facility. In practice, this means a visit of up to 5 days by a handful of inspectors at a time, which amounts to at least 75 inspection days per site in 10 years. However, in many third countries the inspection requirements are much lower than in the EU.

In the USA, for example - where many large (agro)chemical companies are located and therefore many GLP studies are carried out - any laboratory can declare itself as "GLP safe" without the need for an external audit. It is then the task of the US Environmental Protection Agency (U.S.-EPA) to subsequently control and monitor compliance with the GLP standard. In reality, however, this is only done to a very limited extent. This is because for the entire USA, according to a reliable source, only 4 to 5 GLP inspectors are responsible in total. This is the only explanation for the fact that, for example, the GLP laboratories of Monsanto Agricultural Co. were only inspected twice (!) in one decade.[14,15]

GLP loses its effect, just as speed limits lose their effect if (almost) no more speed controls are carried out or if there are no corresponding sanctions.

The LPT scandal has made it clear that even in the EU - despite higher control requirements - the integrity of the GLP system is not always guaranteed and the supposed "security against falsification" of GLP studies is, therefore, deceptive.

The fatal consequences of blind trust in GLP studies, or their overestimation, are also documented in the case of the endocrine disrupting properties of bisphenol A[16]. Here too, the EU authorities have denied for long period of time the proven effect demonstrated in the scientific literature over with reference to the GLP studies supplied by industry.

3. Concluding questions

The LPT scandal raises a number of questions that urgently need to be addressed by the German and European authorities:

(1) Why did the alleged fraudulent manipulation of study results go undetected for at least 15 years, and how many years longer would this have continued if the abuse had not been exposed by an undercover animal welfare activist?

(2) Which pesticide active substances, medicinal products and other chemicals are in circulation throughout the EU whose marketing authorisation was obtained by means of studies carried out at LPT?

(3) What measures have the responsible authorities in the German Länder and the Federal Institute for Risk Assessment BfR (Bundesinstitut für Risikobewertung) taken so far in response to the reported manipulations and falsifications of studies? The BfR is responsible for the nationwide coordination of GLP controls.

(4) According to a reliable source, LPT facilities have been checked by GLP-inspectors up to 2-3 times a year. Have the authorities in northern Germany performed particularly badly or are GLP inspections routinely insufficient throughout Germany? Is this possibly due to understaffing, insufficient qualifications, or are there other reasons?

(5) How is the widespread blind acceptance of GLP studies to be assessed in view of the control failure in Germany, which has become apparent with the concrete example of LPT, and in view of the fundamentally inadequate verification of GLP standards in other important regions of the world, such as the USA.

(6) In view of the apparent inability to ensure compliance with GLP standards, would it not be urgently necessary to eliminate the inherent conflict of interest arising from the fact that the studies are commissioned by manufacturers who have substantial economic interests in the results of these studies?

(7) What would be more effective: a massive increase in GLP controls or a decoupling of industry from regulatory studies? In other words, it should not be the industry, but the authorities that decide which contract laboratory carries out what study. ((the costs would still be borne by the applicant for approval).

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1 Citizens for Science in Pesticide Regulation - A European Coalition. Manifesto: Rigorous science, safe food and a healthy environment: https://www.pan-europe.info/sites/pan-europe.info/files/Citizens%20for%20Science%20in%20Pesticide%20Regulation_Manifesto_FINAL.pdf

2 FAKT broadcast of 15 October 2019: https://www.mdr.de/video/mdr-imersten-videos/c/video-346202.html

3 FAKT broadcast of 5 November 2019: https://www.mdr.de/video/mdr-imersten-videos/c/video-352684.html

4 FAKT broadcast of 26 November 2019: https://www.mdr.de/nachrichten/politik/inland/video-359484_zc-36896c52_zs-8ae77846.html

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