PHAREM

2020-01-14

OFFICIAL STATEMENT: POSITIVE RESULTS BY PCURE IN THE UPPSALA UNIVERSITY HOSPITAL PROJECT. OTHER CONCLUSIONS BASED ON SCIENTIFIC MISCONDUCTS.

Company official positioning:

This official statement has been published to show on the positive results obtained by pCure in the Uppsala University Hospital (UUH) project.

The approach by the UUH project on how the pCure test was performed, the choice of statistical method applied, and the conclusions made in the UUH report are very misleading and border on scientific misconducts. Pharem takes a strong position against how the UUH report has been concluded and do not represent a correct scientific evaluation of the product.

pCure is developed by Pharem Biotech AB with the purpose to offer a simple and complementary product for removing specific pharmaceuticals that are harmful to the environment. This statement report will explain, in a popular science approach, how the effect of pCure can be **verified** using the UUH measurement data either by a correct understanding of the product parameters, a correct interpretation of the statistical methods used or using simple improvements of the statistical methods. Pharem clarifies this position with three main statements against the UUH pCure report:

Statement 1: The effect of pCure can be verified by a better understanding of the mistakes made in the project and the incorrect scope for evaluation

Statement 2: The statistics are poorly performed and understanding the statistical concepts will identify the verified effect by pCure.

Statement 3: Simple improvement of the statistics will amplify the verified effect by pCure

We would also like to point out that an agreement was made prior to the project between Pharem and the research group at UUH, that Pharem could comment on the obtained results but not interfere with a publication. Pharem received no prior knowledge of the publication and had no opportunity to review their results before they went public. Pharem has approached the research group, UUH and the journal to receive answers on the identified mistakes. All contacted parties have refused to give any written answers or have any meetings to address the raised concerns.

With this official statement, Pharem wants to raise concern on the credibility of the report and the peer-review process considering the identified scientific misconducts and that two of the authors are editors on the publishing journal.

The research groups planning, execution and reporting from a scientific and ethical approach is criticised and should raise a concern with any external reviewer.

To learn more, visit:
https://www.pcure.se
https://labs.pcure.se
https://help.pcure.se

Introduction to pCure

We live in a diverse world on a planet with a fragile ecosystem. Human society has made great advances with many benefits for humankind, but also with unwanted side effects. One of the growing concerns is the increase of pharmaceuticals and similar organic micropollutants (OMPs) in our environment. At Pharem, our creativity is fuelled by the urge to find new solutions in the endless unexplored field of biotechnology and our core business is to find treatments to OMPs in water - making this planet a better home for the generations to come.

We believe that the wastewater treatment plant (WWTPs) is a key area to combat OMPs where we offer new technology through our own Pharem Filtration System (PFS). The ambitions are high within the WWTP field, but it will likely only reduce the OMP release into Nature by 30-50%. It is expected to take over a decade to reach even such a goal. A broader scope is needed to faster combat the environmental issue and contribute to reducing the amount of OMPs that reach Nature.

pCure is a product that has been developed for this purpose. pCure is a simple product that can be a complementary solution next to WWTP installations and offer a possibility to approach areas where WWTP installations are not applicable. Though it cannot provide the same scope/effect as PFS and other industrial solutions, it is a simple and low-cost way of reducing a relevant amount of OMPs released from households, healthcare and society. For further details, we refer to http://help.pcure.se

Statement 1: The pCure effect can be verified by understanding misconseptions of product parameters and incorrect evaluation scope.

Issue 1.1: Questionable statements and comparisons

There are recurring issues with many unsupported claims about the product or the science behind it in the report. These are a big no-no in science and surprised how these could go through a peer-review process.

Of serious concern is the project groups claim that there is a lack of supporting publications for enzymatic effect on pharmaceuticals. Not only is the mapping of these effects a necessary part in the development of pharmaceutical APIs[1,2], but is an active and developing field within bioremediation[3,4,5]. A simple google search would have given these answers and the false claim only undermine the concept of the pCure product in a false way.

There is a general discussion within the report which is misleading the reader to believe that pCure is supposed to directly compare to an industrial wastewater installation. The purpose of pCure is to be a complementary solution to industrial solutions or offer a solution where industrial solutions are not feasible.

An area where industrial solutions are not applicable is for the public, and we believe in pCure as a solution that can engage the general public in the environmental topic. Comparing the product with an industrial solution could put an unreasonable expectation on pCure. For industrial solutions, Pharem offers its own product line PFS and would like to point out that it is contradictory to believe we would develop two competing technologies.

Issue 1.2: Using the product under its least active phase

In the UUH project, the goal is to test how the pCure/enzymes can break down specific pharmaceuticals. In any evaluation of a technology or product, it is important to set up the project according to the correct product parameters to get the accurate results. To create a simple metaphor; evaluating a cars acceleration will give very different results if it is tested downhill compared to uphill.

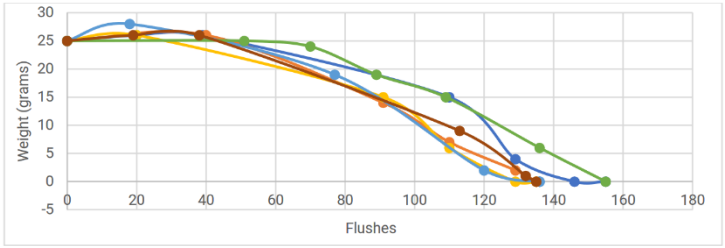

Figure 1. Dissolving behavior for pCure in 8L flush volume toilets. These results are based on industrial standards and performed by Buck-Chemie GmbH and representative for the pCure version used at UUH.

In the pCure project, the issue is that the product was on average only tested during its least active phase, so uphill in the metaphor mentioned above. The effect from pCure come from the release of enzymes into the sewage water by flushing. In Figure 1 is the standard dissolving behaviour for the pCure version used within the UUH project. The dissolving behaviour was determined according to industrial standards by Buck-Chemie GmbH. This information was available to the research group before the project and also communicated during the project. It should also be noted that the dissolving behaviour is typical to rim blocks.

The figure (figure 1) show that there is a slower release during the initial lifetime of the product. This is due to water accumulating into the block mass and softening it up, causing more mass get loose in later flushes, this is a normal behaviour for a toilet rim block. An increase and steadier release of mass can be seen after approximately 50 flushes.

According to the numbers presented in the UUH-report, the average usage of pCure in the UUH project can be calculated to 35-40 flushes. This conclude that pCure was on average used during a period of slower mass release and the effect is expected to be below average.

Issue 1.3: Testing outside the pCure effect definition

There has always been public information available by Pharem on which pharmaceuticals pCure has been developed to have an effect on and shared with the research group. The selection of target pharmaceuticals is based on a list published in Nationella Läkemedelsstrategin[6]. Evaluation of any pharmaceutical outside this list should have no impact on the review of pCure. This can compare to evaluating the effect of a pain killer as a medicine toward headaches based on its effect as a medicine toward cancer.

We do not have an answer to how this could have passed any critical review and the conclusions made in the project are based on effects against pharmaceuticals that have never been in the scope of pCure. Many of these pharmaceuticals are also not considered as a problem for the environment, and there is therefore no reason for pCure to target these pharmaceuticals in the first place. Any technology or product can easily be disproven if tested outside its intended use or effect.

Summary statement 1

We wanted to point out the mistakes in the project statements and approaches that are the most obvious and cause false conclusions. There are more of them not pointed out here and there seem to be a lack of general knowledge about the scientific field. Most of these issues could easily have been resolved by simply asking the researchers behind the product and should not have caused any bias. Any well-informed project will generate a better result.

The approach of the UUH project resulted instead in a misinformed study that tested the product under bad conditions and with a scope that is not relevant for a product review. Looking at the result with only the pharmaceuticals pCure was developed for, effect can be showed with statistical significance. This was even pointed out in the article but disregarded when evaluating the product. Again, any technology or product can easily be disproven if tested outside its intended use or effect.

Statement 2: The statistics are poorly performed and understanding the statistical concepts will identify the verified effect by pCure

Statistics are challenging even at an academic level, but we will try to explain the mistakes made in the UUH report as simple as possible. The idea behind statistics is that it is practically impossible to measure everything, so instead, you take samples and apply statistics to get a result that is as close to the actual or true result as possible. In our case, this would mean it is impossible to measure every drop of water, and instead, you measure samples that you statistically try to figure out the true result from. But measurements and data can come in many forms, so it is equally important that you apply the correct statistics. Using multiplication where you are supposed to use addition would simply give you bad results.

Issue 2.1 Not understanding effects from distribution, mean and median

There are several issues with the statistics in the report and we will go through the important ones. Most of the issues stem from not fully understanding the effect on statistics by the distribution, mean and median. They touch upon mean and median in the report, but not about data distribution.

Data distribution can come in many forms and is telling us about how the values are spread out. The most common distribution is a “normal distribution” where you will have an equal spread of values around an average value. Therefore, much of the statistics out there are based on the data being normally distributed. The data from this project however, is not normally distributed. According to statistics (yes there are even statistics on the type of distribution) it is something named “log-skewed distribution”. This is of importance to understand what type of statistics that are relevant to use and what result based on mean or median is relevant to use.

In general, mean is considered a better value than the median to estimate the true value, and this is true for a normal distribution. But in a skewed distribution, as in this project, the mean start to go far away from the true value due to outliers and the median will quickly become a better estimate of the true value. This can be exemplified in something termed the Bill Gates problem[7].

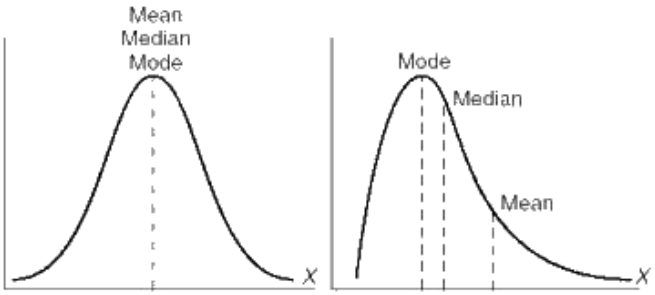

Figure 2. Visualization of normal distribution (left) and skewed distribution (right) and how different estimates position in those distributions

Example of the Bill Gates problem:
Imagine you want to estimate the income of an average person, so you randomly select 100 people for this evaluation. By random, 1 person of the 100 selected is Bill Gates. Using the average income data with Bill Gates included would cause your result to conclude the income for an average person to be >10 million dollars. We can with confidence say this is false, and it is because Bill Gates within the sample set will strongly skew the data. If we instead look at the median value, we will get a value closer to the true value. Median values are more accurate than mean values in skewed data distribution.

In the UUH report, it is therefore important to understand the data is strongly skewed. All statistics based on mean values (mean and t-test/parametric) will therefore not give good results simply because they are the wrong type of statistics. This does not mean that you could eventually use this type of statistics, but will require a rework of the data and we will discuss this in a later segment. As it is presented in the report, all results based on mean-values should simply be disregarded.

Issue 2.2 The misuse of significance-values

The most problematic issue about the statistics in the report is the misuse of significance and P-value. Most common result to find in a report is the estimated effect in combination of a deviation value. This is weakly represented in the report and demands the reader to make their own calculations and/or interpretations to get this information. The discussion of the UUH report emphasises instead on the P-value (which is one of several ways to calculate statistical significance)

The UUH group are not the first to misunderstand the concept of P-value, but happens so often that the world largest statistical association, American Statistical Association (ASA), has gone out with a statement regarding its misuse and misunderstanding. We will use this statement [8] as the basis for our clarifications.

The first clarification from the ASA statement:

- *P*-values indicate how incompatible the data are with a statistical model.

This explains that a P-value is a measure of how the statistical methods used can correctly show that the measured effect is real. That means if the wrong statistical method is used, you will get a bad P-value, not because the effect is not there, but because the statistical method is wrong. And as we clarified in the previous segment, much of the statistics are poorly applied giving rise to many bad P-values that has nothing to do with effects by pCure.

The following clarifications from the ASA statement touch upon a common aspect:

- Scientific conclusions should not be based only on whether a *P*-value passes a certain threshold
- A *P*-value, or statistical significance, does not measure the size of an effect or the importance of the results.
- By itself, a *P*-value does not provide a good measure of evidence regarding a model or hypothesis.

The UUH report states their claim solely on P-values, exactly what ASA is descibing is not a good measure for a conclusion. A bad P-value can be a result of several things, e.g. bad statistical method, high variation in data, low/no effect, an insufficient number of data points or several other reasons. No effect is only one of many possibilities and without more information, it is impossible to decide which. As we touched upon before, the report leaves a lot of this information unclarified. Stating no effect based on only P-values is considered as one of the main misuses in statistics and even listed at Wikipedia[9] and described in detail by ASA [8].

We would also like to touch upon the theory behind errors in statistics and why statistical significance is of importance. Within this theory, there is more information that can be used to further clarify the mistakes done in the UUH report.
The errors possible when looking at statistics are summarised as Type 1 and Type II errors:

- **Type I**: An incorrect rejection of a true null hypothesis (e.g. Wrongly estimate pCure has an effect)
- **Type II**: A failure to reject a false null hypothesis (e.g. Wrongly estimate that pCure has no effect)

Possibility of Type I error can be calculated by statistical significance (e.g. P-value). A good significance value lets you be confident the measured effect is a true value. But keep in mind that a bad value do not automatically mean no effect, but can be the result of many factors.

Possibility of Type II error can be calculated by statistical power. This is considered of less importance due to a good significance can be achieved with or without a good statistical power. But a bad statistical significance can be described by a bad statistical power.

Bad statistical power indicates often a bad method used for calculation, high variation or too few samples, concluding that even if you have a real effect, you will most likely not be able to identify this (you will receive bad P-values due to bad statistics and/or data). We have concluded that the UUH-report are using bad statistics and we should be able to identify this with bad values for statistical power. We will explore this more closely under statement 3.

Summary statement 2

There are many different calculations made in the report based on several types of statistical methods. It will be hard for anyone not well-versed in statistics to understand which results are of importance or not. This is further complicated by the inclusion of many pharmaceuticals that the product has never been designed to break down. There might be a scientific curiosity to look at these in general, but have no value when evaluating a product claim.

We want to try and simplify the interpretation of the data by looking at the main methods used. The significance calculations by t-test/parametric (assume normal distribution) and Wilcoxon rank test/non-parametric (do not assume normal distribution), which are applied on mean (assume normal distribution) and median (do not assume normal distribution) values. By keeping the earlier segments in this statement in mind, we would like to try and interpret the results presented by the UUH-report.

Let us first refer to table 1 in the UUH report. Referring to what we know about distribution, it is according to expectations that non-parametric results are better than the parametric results. Since most are pharmaceuticals outside of the product claims, a majority of the result presented in this table are of little importance. (We will examine this closer in statement 3)

In table 2 of the UUH report (Figure 3) there is a summarisation of the different pharmaceuticals. All results based on pharmaceuticals outside of the product definition should not be considered for evaluation of the product. All results based on mean results should be disregarded since the data is not normally distributed. We agree with the UUH report that data based on >LOQ data give a better basis for evaluation. Summarising this, there is one segment of the results that is more relevant for evaluating the product than any other segment (circled in red in Figure 3).

		Samples <LOQ considered as = LOQ						Only values >LOQ included in analysis					
		Means			Medians			Means			Medians		
	APIs detected in	Ratio	p Par	p NPar	Ratio	p Par	p NPar	Ratio	p Par	p NPar	Ratio	p Par	p NPar
All APIs	>90% of samples	0.90 (n = 12)	0.4325	0.3394	0.88 (n = 12)	0.2373	0.2661	0.89 (n = 12)	0.3611	0.2334	0.87 (n = 12)	0.1074	0.1514
	>75% of samples	0.97 (n = 20)	0.8013	0.4749	1.13 (n = 20)	0.3775	0.9563	0.92 (n = 20)	0.3893	0.2943	0.95 (n = 20)	0.4102	0.4524
	>50% of samples	1.02 (n = 28)	0.8535	0.3252	1.10 (n = 28)	0.3668	0.8246	0.96 (n = 28)	0.7221	0.2527	0.95 (n = 28)	0.3404	0.3142
	All samples	1.50 (n = 51)	0.2056	0.8390	1.10 (n = 51)	0.1615	0.7305	1.81 (n = 48)	0.1340	0.8007	1.27 (n = 48)	0.2020	0.2052
APIs for which	>90% of samples	1.05 (n = 7)	0.7892	0.9375	0.78 (n = 7)	0.0631	0.0781	1.04 (n = 7)	0.8273	0.9375	0.83 (n = 7)	0.0325	0.0469
Pharem Biotech	>75% of samples	0.97 (n = 9)	0.8226	0.5703	0.83 (n = 9)	0.0645	0.0977	0.95 (n = 9)	0.7208	0.4258	0.85 (n = 9)	0.0174	0.0195
states pCure is	>50% of samples	0.96 (n = 10)	0.7526	0.4316	0.84 (n = 10)	0.0469	0.0488	0.93 (n = 10)	0.6146	0.3223	0.85 (n = 10)	0.0117	0.0098
effective	All samples	2.40 (n = 13)	0.3495	0.7869	0.87 (n = 13)	0.0493	0.0488	2.67 (n = 12)	0.3581	0.5693	0.89 (n = 12)	0.0404	0.0640

Figure 3. An extract from UUH report showing on the statistics results on ratio effect of pCure. Values>LOQ are of higher relevance. Only APIs in the pCure definition should be considered for evaluation. Median result has higher relevance than mean result due to strong skewed distribution. The most relevant data for evaluating pCure is thus marked with a red square and no scientific argument for the relevance of other data can be identified.

By understanding the concepts behind the statistical methods used, we can circle in on the results that are most valid for evaluating the product. There should not be a need for method variations, a mix of mean and median, and all these unnecessary calculations are only confusing the reader and have apparently confused the UUH group behind the article.

Looking at the relevant data there is only positive results, with statistical significance. The parametric (normal distribution) value also give significance, likely due to that the distribution of the median values are closer to a normal distribution. The unexpected low effects are likely due to the experimental design that has been criticised in statement 1.

Statement 3: Simple improvements of the statistics will amplify the verified effect by pCure

We want to explore the concept of statistical power further. Median and non-parametric results are of higher relevance when the data is strongly skewed, as in the UUH-report, and these result show statistical significance. When not skewed or deviating strongly from normal distribution, both mean and parametric tests will give a higher statistical power. This is why it is common in statistics to try and treat/transform data to still be able to apply mean and parametric tests.

We would like to exemplify a common method used in statistics to remove outliers or “Bill Gates” effect and how this will give significantly improved data-set. We will show how the statistical power improve after this type of adjustment and the result then start to be similar to the median/non-parametric results. We will also clarify that we exclude any substance outside of the pCure definition since it has no relevance for the evaluation of the product definition.

Statistical power and cut-off

The statistical power describes the possibility of Type II error in statistics. It is similarly calculated between 0 to 1 but with the wanted result as high as possible. An arbitrary threshold generally used is >0.8. In general, it is describing how well the experimental/statistical approach is at identifying effects. Important values to calculate this are effect size, sample size, variation and desired significance. (For theoretical reasons an arbitrary effect of 50% is used)

Looking at the statistical power of the mean based parametric test (Table 1), the highest value is 0,487 with most of them being much lower. This means that the method used likely will cause Type II error, aka, not identifying an effect when there is an effect. These are the methods that UUH-report base their conclusions on. As an effect of this, results are all over the place, and P-values are far from good.

We would like to treat the data with a common statistical method, cut-off. This is a method commonly used to remove outliers and a version of this has already been used by the UUH-report (Figure 3*, n<50%, 75%, 90%*). Median is for example a version of a 50% cut-off, where the middle value is left as the result. For general public, cut-offs are known in sports where judges give points, and the lowest and highest value are removed to prevent biased data from affecting the average result. We would like to apply a 10% cut-off and evaluate the effect this has on the results. Similar to sports, you remove from both the lowest and highest results to prevent a biased effect.

The summary of the results can be seen in table 1. We want to point out how much the results are improved by such a simple and common statistical approach. It enhance the previous argument that any mean/parametric result based on raw data (prior to cut-off) is not normally distributed and lack any relevance for evaluation of pCure.

Looking at each pharmaceutical seperately, the data is drastically improved (higher statistical power) after a 10% cut-off, even though most are still of low quality (Statical power<0.8). It is still enough to start seeing the expected results and are more according to what could be expected in these experimental circumstances and closer to the median results. Some of these effects also attain statistical significance, concluding high evidence that the product work against these substances.

Table 1. A comparison between the mean values of the untreated raw data and treated data with a 10% cut-off. Effects are presented as percentual change over time. Negative values means removal and positive values means increase. A T-test was used as the parametric test. The statistical power has been calculated on the control values with a prior expectation of 50% removal. Median values for the evaluation of overall effect is added as comparison.

Compound	Untreated (raw) data					Treated data (10% cut-off)				
	Avg. Sample size group (n)	Effect, Mean (%)	Effect, Median (%)	P Par	Stat. pow. (50% red.)	Avg. Sample size group (n)	Effect, Mean (%)	Effect, Median (%)	P Par	Stat. pow. (50% red.)
Carbamazepine	43	**88**	-30	0.3	0.405	35	**5.2**	-30	0.831	0.653
Ciprofloxacin	47	**25**	2	0.81	0.103	37	**-10**	2	0.657	0.506
Citalopram	47	**-0.2**	-1	0.996	0.351	37	**-30**	-1	**0.068**	0.697
Clarithromycinn	<1	**n.d.**	n.d.	n.d.	n.d.	<1	**n.d.**	n.d.	n.d.	n.d.
Diclofenac	32	**-15**	-8	0.676	0.189	24	**14**	-8	0.548	0.593
Fluconazole	44	**-45**	-43	0.269	0.169	36	**-45**	-43	**0.02**	0.6
Metoprolol	47	**7.2**	-27	0.878	0.487	37	**-28**	-27	**0.029**	0.895
Oxazepam	47	**-19**	-4	0.664	0.168	37	**-10**	-4	0.49	0.942
Sertraline	18	**-9**	11	0.838	0.216	12	**-14**	11	0.569	0.322
Sulfamethoxazole	40	**-41**	-15	0.47	0.116	30	**-21**	-15	0.619	0.15
Tramadol	40	**-32**	-1	0.302	0.247	32	**-8**	-1	0.634	0.739
Trimethoprim	47	**-26**	-19	0.414	0.326	37	**-31**	-19	**0.09**	0.577
Erythromycin	5	**2084**	6	0.626	0.114	2	**14**	6	0.796	0.114
All compounds with detection in	**Sample size group**	**Effect, Mean (%)**	**Effect, Median (%)**	**P Par Mean**	**P Par Median**	**Sample size group**	**Effect, Mean (%)**	**Effect, Median (%)**	**P Par Mean**	**P Par Median**
>90% of samples	7	**4**	-17	0.827	**0.033**	7	**-21**	-17	**0.016**	0.033
>75% of samples	9	**-5**	-15	0.721	**0.017**	9	**-20**	-15	**0.005**	0.017
>50% of samples	10	**-6**	-15	0.615	**0.012**	10	**-16**	-15	**0.019**	0.012
All samples	12 (13)	**268**	-11	0.357	**0.040**	12 (13)	**-14**	-11	**0.027**	0.040

When examining the results for the calculation over all pharmaceuticals, we have previously concluded that the only relevant results are median based calculations. Here we can see that with a 10% cut-off, the result for mean based calculations are similar to median results and with very good statistical significance. This is expected when the data distribution is starting to get closer to a normal distribution, which is the purpose of a cut-off.

In the end, it did not take more than a common statistical method to show that the effects by pCure are present with a statistical significance based on both mean and median values.

Summary statement 3

In general, low statistical power means that it will be hard to establish statistical significance (*P*-value), not due to lack of effect, but because of bad data/method quality. This should have been identified by the research group. Simple methods improve the underlying data and it is possible that more advanced methods could result in even better estimates of the effect.

We have in this and earlier statement showed that while untreated and with the identified distribution, the only relevant result (non-parametric/median) shows an effect by pCure with statistical significance. We have also shown that a common statistical method to remove outliers in the data, improve the quality (statistical power) of the data and the following outcome of parametric/mean result become similar the non-parametric/median results with effect by pCure and statistical significance. The unexpected low effect can be described by statement 1.

In summary, we can show with simple improvements of the statistical methods that both parametric/mean results and non-parametric/median results show an effect from pCure with statistical significance.

Summary Statement Report

Pharem is a small company that with hard work from our personnel, wish to make the world a better place. A bit of critical scrutiny is healthy and prevent us from making mistakes. It is therefore unfortunate that a report (UUH report) of low quality has not received the same critical scrutiny.

The scientific approach of the UUH report is under all criticism when simple statements (e.g. enzyme effect on pharmaceuticals) can easily be disproven by a google search. Their statistical mistakes are based on basic misuses of statistics even listed at Wikipedia and pointed out in detail by official statements from the world largest statistical associations.

We have tried to lift these issues with the involved parties but has been refused to any type of oral or written dialogue and still not received any answers on a single issue raised. We want to communicate these issues in this report in a popular science approach to invite others to understand the issues raised. We encourage anyone to critically review the UUH-report or contact us if you are interested in more details or a more in-depth scientific explanation.

Our biggest regret is the delaying effect this has on realising a solution that we believe can do something great for the environment and that is easy to implement anywhere. We are thankful to all our employees and partners that have seen through these theatrics and continue to support Pharem in its endeavours.

In summary, Pharem takes a strong position against the conclusions in the UUH report and strongly question how this report has gone through a peer-reviewed process with all the evident mistakes. We also clarify that effects by pCure are present by any scientific standard within the report. The effect from pCure can be verified with statistical significance by correct interpretation of the results or by simple improvements of the data. We encourage anyone that read the UUH report to view it with the same critical scrutiny as is expected when looking at our work.

References:

[1] C. Ionesco and M. R. Caira (2005) Drug Metabolism: Current Topics, Springer Netherlands.

[2] The Drugbank: https://www.drugbank.ca/ Accessed 190117

[3] Sharma, Dangi, Shukla. Contemporary enzyme based technologies for bioremediation: A review. *J Environ Manage. 2018 Mar 15;210:10-22.* doi: 10.1016/j.jenvman.2017.12.075. Epub *2018 Jan 10.*

[4] Jerzy Dec and Jean-Marc Bollag, Use of Enzymes in Bioremediation *Pesticide Biotransformation in Plants and Microorganisms, Chapter 10, pp 182–193* DOI: 10.1021/bk-2001-0777.ch010

[5] Jie Yang1, Wenjuan Li, Tzi Bun Ng, Xiangzhen Deng, Juan Lin and Xiuyun Ye, Laccases: Production, Expression Regulation, and Applications in Pharmaceutical Biodegradation, *Front. Microbiol., 16 May 2017* | https://doi.org/10.3389/fmicb.2017.00832

[6] Nationella läkemedelsstrategin, NLS, 2015: https://lakemedelsverket.se/upload/nyheter/2015/miljoindikatorer-rapport-NLS_2015-09-07.pdf

[7] Introductory statistics: When Bill Gates walks into a bar https://introductorystats.wordpress.com/2011/09/04/when-bill-gates-walks-into-a-bar/

[8] Ronald L. Wasserstein & Nicole A. Lazar (2016) The ASA Statement on *p*-Values: Context, Process, and Purpose, The American Statistician, 70:2, 129-133, DOI:10.1080/00031305.2016.1154108

[9] Misuse of statistics, Wikipedia, 2020-01-14: https://en.wikipedia.org/wiki/Misuse_of_statistics#Proof_of_the_null_hypothesis