Baker IDI
HEART & DIABETES INSTITUTE

OMNIBLEND INNOVATION (A PRE-MEAL DRINK) AND IMPROVED GLYCAEMIC CONTROL IN TYPE 2 DIABETES

– THE ACUTE STUDY

Introduction:

At least 50% of people with type 2 diabetes have poor glucose control despite drug treatment and are often faced with the prospect of the addition of another oral drug. Medical nutrition therapy (MNT) advocating eating behaviour and lifestyle modification is recommended as the first line of management for this disease and can also have profound effects on glucose control.

The long-term goals of MNT (Dietitians Association of Australia 2006) are to;

- attain adequate weight reduction,
- achieve optimal glycaemic control (HbA1c < 6.0; fasting glucose < 6.0mmol/L),
- control lipid and blood pressure levels within normal ranges

However, patient compliance is often poor. Dietary strategies include modifications in fat and complex carbohydrate intake or low glycaemic index (GI) diets, all of which can be difficult to follow or sustain (Brekke et al. 2004). An alternative approach is the use of the *Omniblend* (the protein/fibre premeal drink) drink which purportedly reduces gastric emptying and increases insulin release.

Phase 2 of the Omniblend study involved an acute study in five subjects with impaired glucose tolerance (pre-diabetic) and not on medications. In this study the 'premeal drink' converted a high GI food – white bread (published GI=70) to a low GI bread with a GI of 40 using finger prick (the gold standard diagnostic method for assessing blood glucose) or to a GI of 43 using continuous glucose monitoring following ingestion of the pre-meal drink. Peak glucose values were lowered by 1.3 mmol/L. In a much broader population of people, with moderately well controlled type 2 diabetes (HbA1c<8.5% and fasting glucose<10 mmol/L), a similar peak reduction of 1.0 mmol/L was shown by continuous glucose monitoring system (CGMS), and 2.0 mmol/L by finger prick. Thus, the *Omniblend* drink appears to be effective at reducing the peak glucose by about 1 mmol/L and average glucose over 3 hours by 0.7-8 mmol/L. The latter change, if maintained over all 3 meals, would lower HbA1c by about 0.4-0.5% (Gannon et al 2003). This is equivalent to the effect of combination oral hypoglycaemic agents such as the addition of gliptins to metformin. Either finger prick blood glucose levels (BGL) or CGMS could be used to assess the acute effects of the drink.

Methods

Subject selection is described separately in each phase. The study was a 7-day continuous glucose monitoring (CGMS)study where glucose levels were measured every 15 minutes. Four finger prick tests were also conducted per day for optimal performance. Six visits to the Baker IDI were required with the first day for insertion and stabilisation of the CGMS and the next 4 days for meal/drink tests. A pre-test meal was provided the night before each test to standardise conditions. All morning medications were taken at least 15 minutes before the test drink. The breakfast test meal at the Centre consisted of 2 slices of bread, margarine and jam (3 slices for men) plus tea/coffee if desired, with a drink 15 minutes beforehand. This drink consisted of 150ml of cold water mixed with 20g of protein plus 5g of fibre (*Omniblend* the test drink) or 150ml of plain cold water (control). The order of these two pre-meal drinks was selected at random. The test drink was taken on two of these days, and water on the other two days. Following the breakfast test meal, finger prick glucose measurements were taken every 15 min for the first hour, then at 90 min, 120 min and 180 min. For visits on day 5 and 6, 2 further breakfast test meals were supplied to consume at home, each consisting of 4 slices of plain white bread with no jam or margarine, with a shake to be consumed 15 mins prior to the meal on one of these days. These 'at home' tests were usually be done on a Saturday and Sunday. Multiple finger pricks in the 3 hours following the 'at home' meal tests were not required, nor for the pre-test meal.

The GI of the meal was given an arbitrary value of 70 based on white bread alone. Almost certainly the addition of margarine and jam (GI of about 50) will reduce GI. The average BGLs over 3 hours was determined with and without the drink and the effect computed as average BGL drink/average BGL control meal. This was then multiplied by 70 to produce the computed GI of the meal preceded by the drink.

Phase 1.

The first 7 volunteers all had poorly controlled type 2 diabetes and were on medications. The average fasting BGL over 4 days was ≥ 9 mmol/L (5 averaged over 10 mmol/L for the whole period). They all underwent 4 separate tests of ingesting 4 slices/bread (about 80g of carbohydrate) preceded 15 min before by the protein shake- *Omniblend,* of various flavours or water. CGMS was performed for 4 complete days. In this group peak meal responses were very variable and sometimes, varying significantly from 1 to 11.7 mmol/L. Average 4-hours BGL after ingestion of the *Omniblend* -shake (or water) varied from 9.3 to 16.6 mmol/L so all the volunteers had poor control. The average difference in favour of the drink was only 0.15 mmol/L (p=0.58).

Following these results, a decision was made to amend the protocol to only recruit pre-diabetic or newly diagnosed diabetics (<2 years) with good glycemic control and to make sure medications (if any) were taken at least 15 minutes before the drink and this was documented appropriately. Four clear hours was left after the meal before further food was taken. In addition the CGMS was allowed to stabilise overnight before using it for further tests.

Phase 2.

For this phase, 5 subjects with pre-diabetes were recruited. One may have had diabetes based on postprandial BGL of over 11.1 whilst one appeared to be quite normal (fasting gBGL<5, average postprandial BGL <7 mmol/L). Average fasting BGL was 5-6 mmol/L. The average difference in peak glucose responses between water and shake was 1.3 mmol/L by CGMS (p=0.04). Finger prick samples were also done over 180 minutes for these 5 subjects and the average effect of the drink on peak BGL was a reduction of 1.7 mmol/l (p=0.014). Figures 2-6 show the finger prick and CGMS BGL values. The difference between the drink and placebo area-under-curves was very similar for the two methods even though the fingerprick glucose levels were higher. The drink thus has the effect of reducing white bread from a high GI food with a GI of 70 to a low GI food with a GI of 40-43. With an average reduction in finger prick BGL over 3 hours from 8.2 to 7.5 mmol/L would, if maintained over all 3 meals, be reflected in an HbA1c fall of 0.4% from 7 to 6.6% (see http://www.ngsp.org/convert1.asp). Similar results can be seen in the meal studies of Gannon et al 2003 where a high protein diet reduced meal peaks by 0.4-0.5 mmol/L and 24 h area by 13 mmol/l/h (reduction of 0.5 mmol/l each h) and resulted in an HbA1c reduction of 0.5%.

The CGMS values for 4 hours post *Omniblend* -shake or water ingestion for these 5 subjects was combined (48 data points for each day) over 4 days. There was a strong time effect (F=12, p<0.0001) and diet by time effect (F=6.2 p<0.0001) showing that the drink had a very significant effect over 4 hours.

Figure 1 below shows the CGMS curves combined from the 5 subjects over 4 hours with the peak pushed out from number 15 to number 23 (a 30 minute shift from 60 minutes to 90 minutes) and 1.3 mol/L lower. The values at 2 hours though were similar.

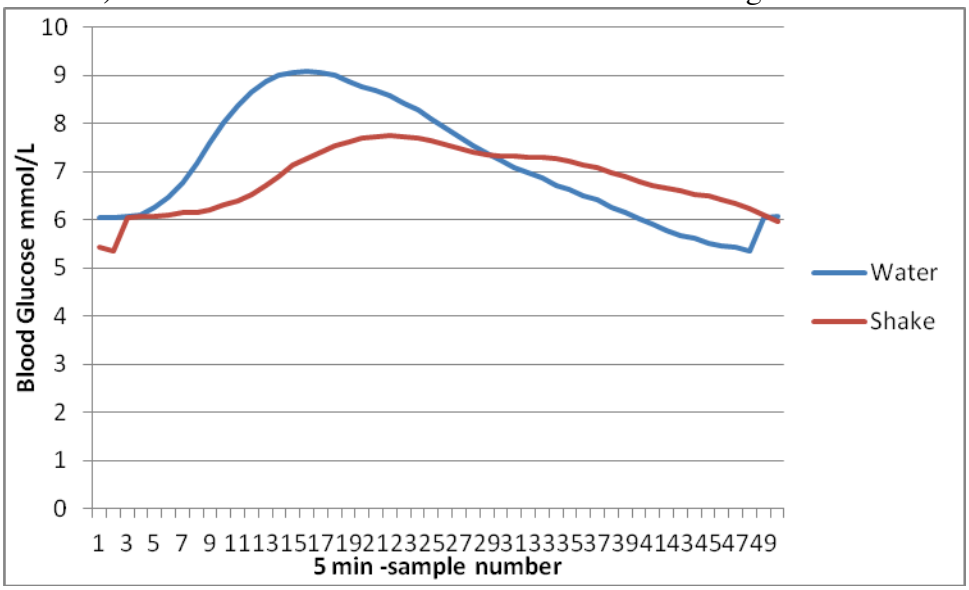


Figure 1: CGMS concentration curves over 4 hours (n=5 subjects)

Figures 2-6 show results for each individual with values for both fingerprick glucose (BSL) and CGMS glucose

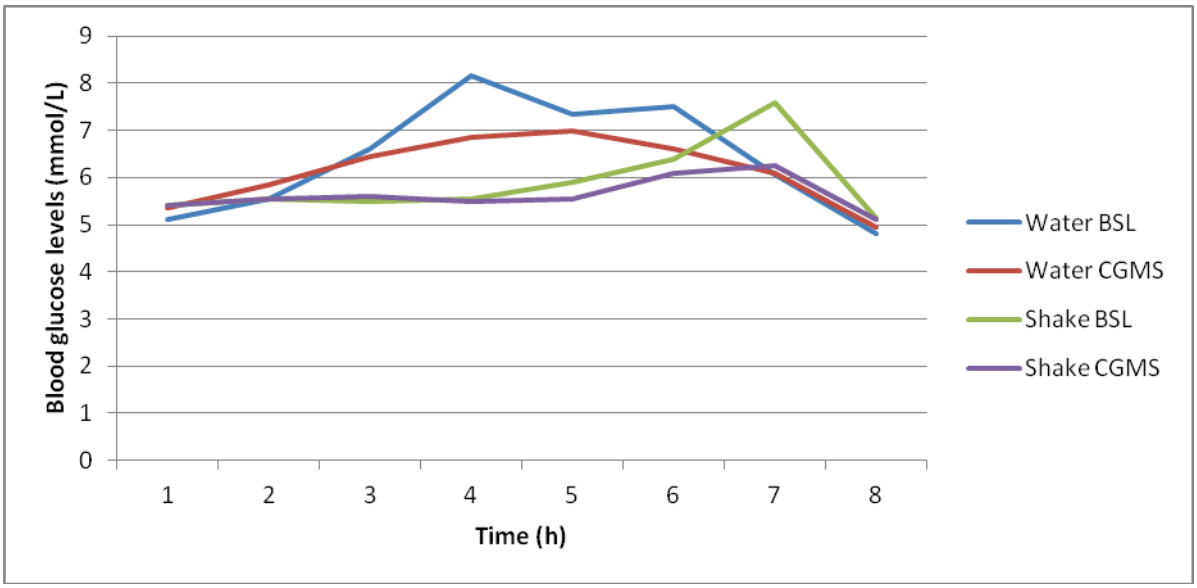
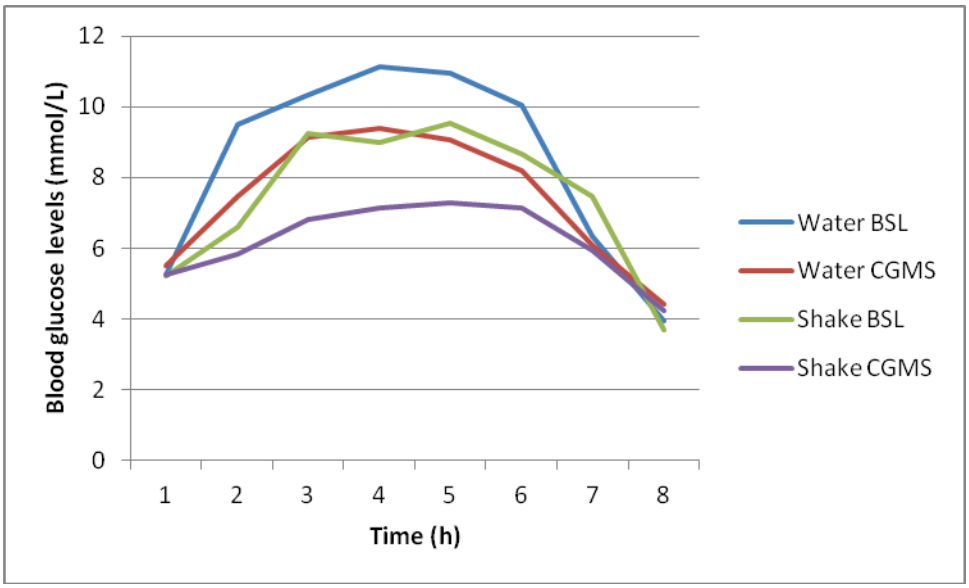


Figure 2. Subject 1



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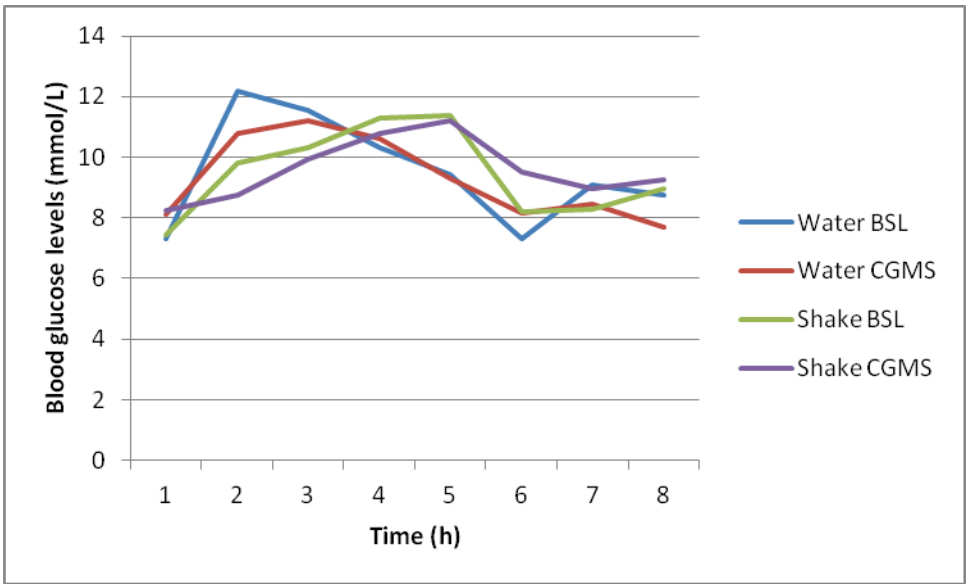

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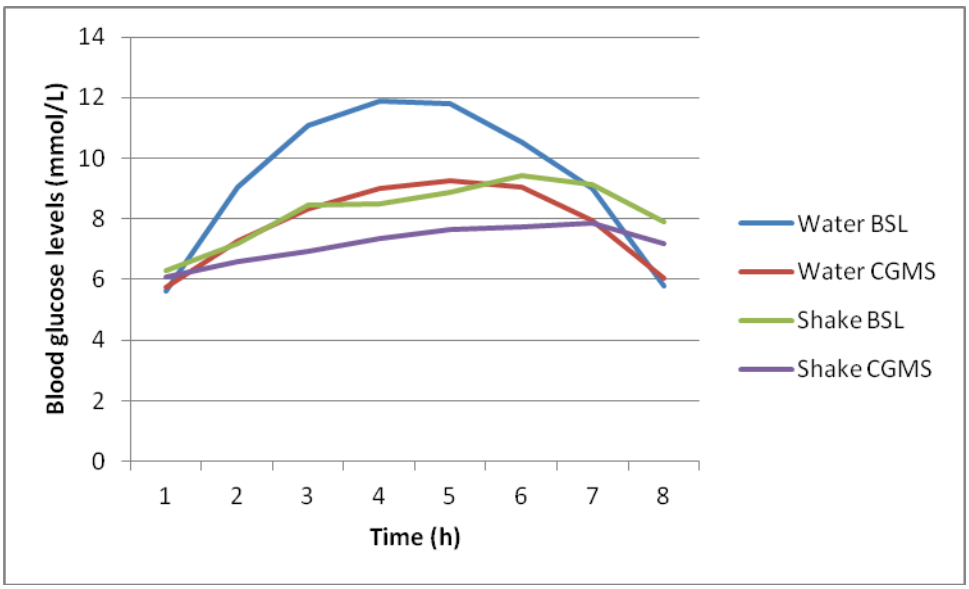


Figure 5. Subject 4

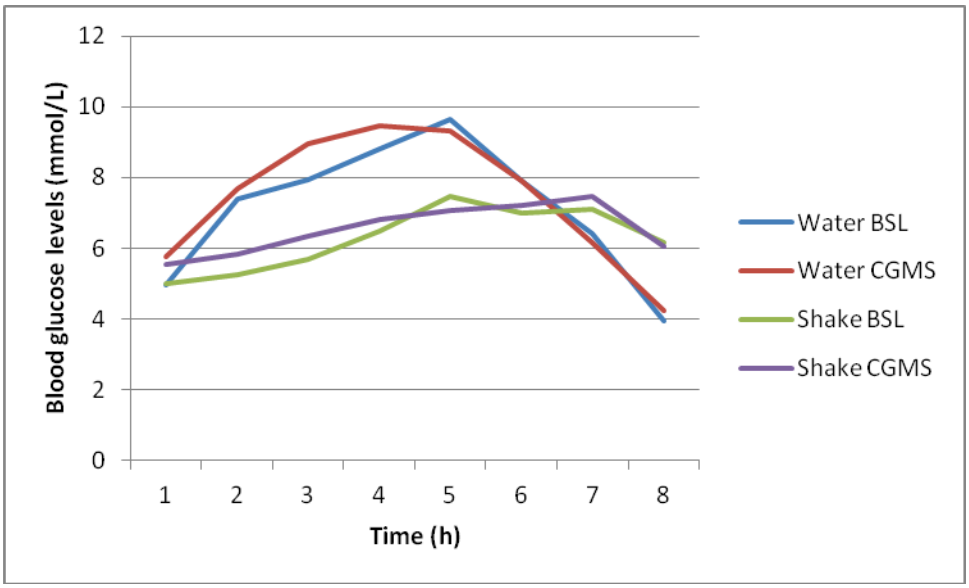


Figure 6. Subject 5

The results in Figure 7 combined data for all 5 subjects

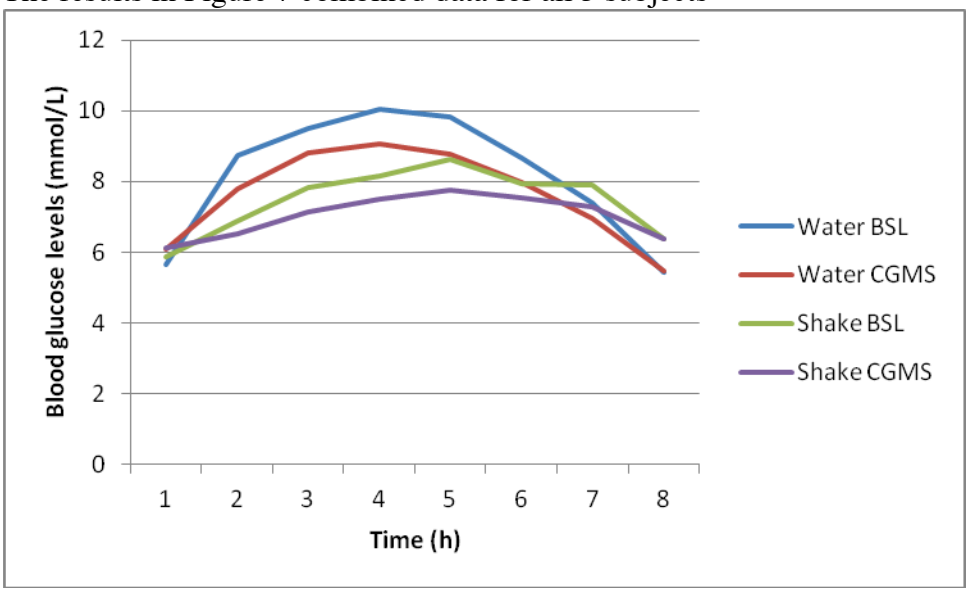
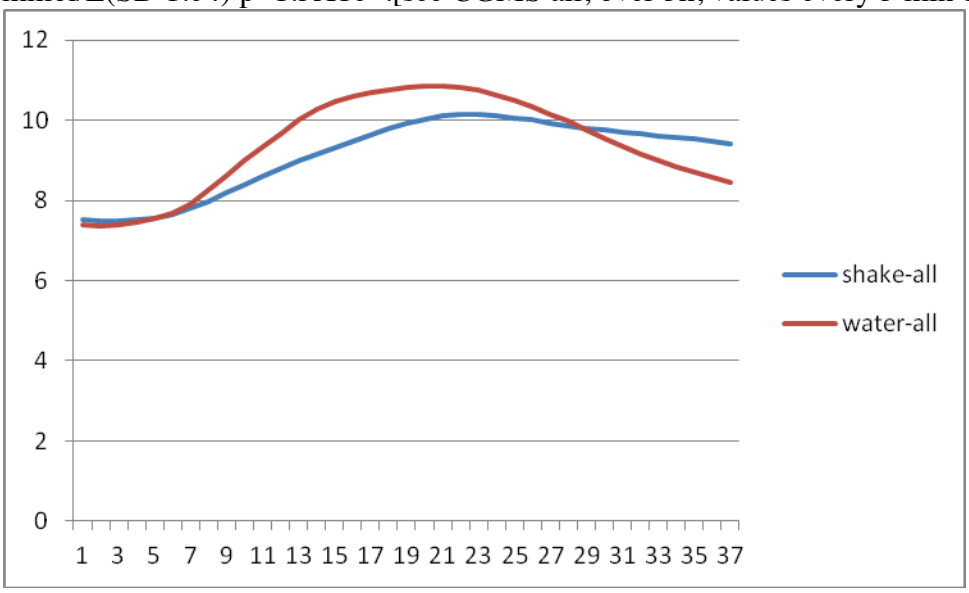


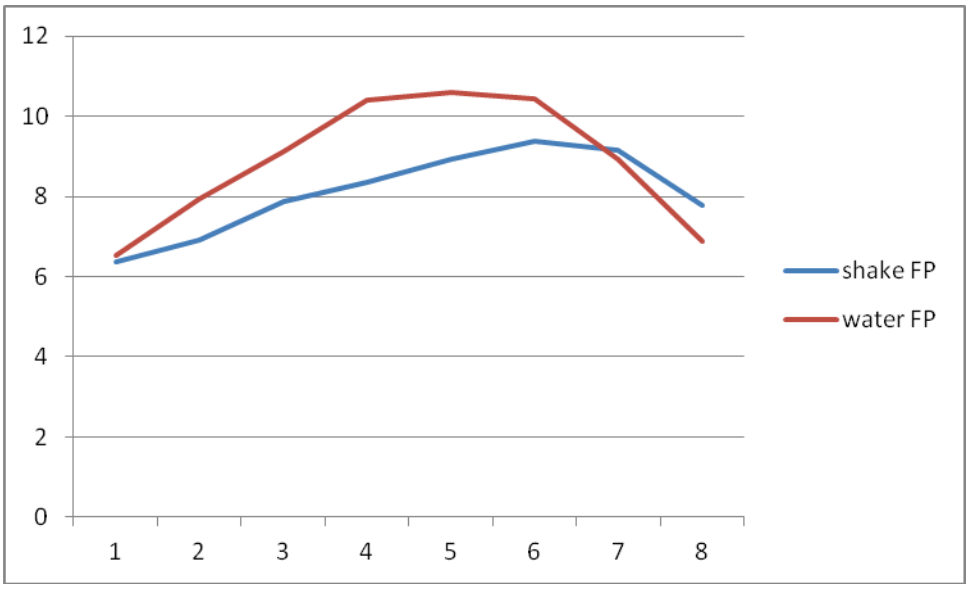
Figure 7. Combined data for n=5.

Phase 3.

Following the successful completion of the first 5 participants, another 19 subjects with pre-diabetes or moderately well -controlled type 2 diabetes (fasting glucose<10 and HbA1c<8.5%) were recruited. These participants consisted of 12 people with type 2 DM and 7 with prediabetes. One subject had an average fasting BGL of 10.1 mmol/L while all the rest were under 9 mmol/L. Those taking medications were instructed to take their medications at least 15 minutes before the drink to avoid any carry-over effects of the drug. There was no difference in response between the people with type 2 DM and prediabetes and there was no relationship between fasting glucose response and the effect of the drink. The average effect of the drink for subjects in phase 2 and 3 was a peak reduction of 1.04 mmol/L (SD 0.88, $p=3X\ 10^{-5}$) with the effect ranging from +1.3 mmol/L to -2.3 mmol/L. The average CGMS glucose over 3 hours was lowered by 0.7 mmol/L. If all subjects tested, including those in phase 1, were combined (n=31) then the overall effect was a peak lowering of 0.84 mmol/L(SD 1.04) $p=1.5X10^{-4}$.[see CGMS all, over 3h, values every 5 min below]



Looking at the finger prick test results at 0, 15, 30, 45, 60, 90, 120 and 180 minutes (data points 0 to 8) in 22 individuals then peak BGL was reduced by 1.1 mmol/l at 15 min (p=0.003), 1.3 mmol/L at 30 min (p=0.001), 2.1 mmol/L at 45 min ($p =7\ x10^{-5}$) and 1.7 mmol/L at 60 minutes (p=0.0007) and 1 mmol/L at 90 min (p=0.02). It was higher by 0.25 mmol/L at 120 min (NS) and 0.84 mmol/L at 180 min (p=0.003). Average glucose over 3 hours was reduced by 0.77 mmol/L (p=0.0003)[see FP all graph below]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Discussion.

The premeal protein/fibre drink- *Omniblend* -lowers the average glucose over 3 hours by 0.7 mmol/L and peak glucose by 1 mmol/L by CGMS and 0.77 mmol/l average and peak glucose by 2 mmol/L by fingerprick. This is equivalent to the effect of a drug such as the gliptins which lower HbA1c by 0.4-0.5% when added to metformin. In 901 free living, patients with type 2 diabetes those in the lowest quintile of glycemic index and glycemic load had an HbA1c 1% lower than those in the highest quintile and the difference in 1h glucose between these groups of about 2 mmol/L(Esposito 2010). Thus a reduction in peak (or 1hr) glucose of 1 mmol/L equates to a 0.5% lower HbA1c. In the Canadian Low GI trial, 2hr glucose was 7% lower in an oral glucose tolerance test at 12 months but HBa1c was not different (Wolever 2008). A meta-analysis of 16 studies using GI in meal planning showed an average reduction in HbA1c of 0.27% (p=0.03) and fructosamine by 0.1 mmol/L (p=0.05) (Opperman 2004). This treatment (*Omniblend*)would appear to outperform low GI meal planning but long term data is not yet available. In the Jenkins 'low GI- 6 month study' in type 2 diabetes (2008), Hba1c was lowered by 0.32%. The difference between the diets was 13GI units or about 20% which is less than the breakfast meal change in this study.

In terms of cardiovascular complications a 1 hour postprandial glucose level predicts myocardial infarction and death in newly diagnosed people with type 2 diabetes (Hanefeld 1996). In both men and women with diabetes who had myocardial infarctions a post lunch difference of about 2 mmol/L (time not specified) was seen compared with people without disease (Cabalot 2006). In a meta- analysis of 7 acarbose studies (*alpha*-glucosidase inhibitor which reduces glucose absorption) 1 hour postprandial glucose was reduced by 1.6mmol/L and 2 h glucose by 2.2 mmol/l while HbA1c was reduced by 0.6% and myocardial infarctions were reduced by 64%. Acarbose also reduced weight, triglyceride and systolic blood pressure (Hanefield 2004). Thus in this study a 1mmol/L reduction in peak glucose could if maintained over the long-term could reduce HbA1c by 0.4% and potentially lower myocardial infarctions by 16% (assuming half of the acrabose effects is due to glucose and the other half dye to weight, BO and triglyceride reductions acarbose effect).

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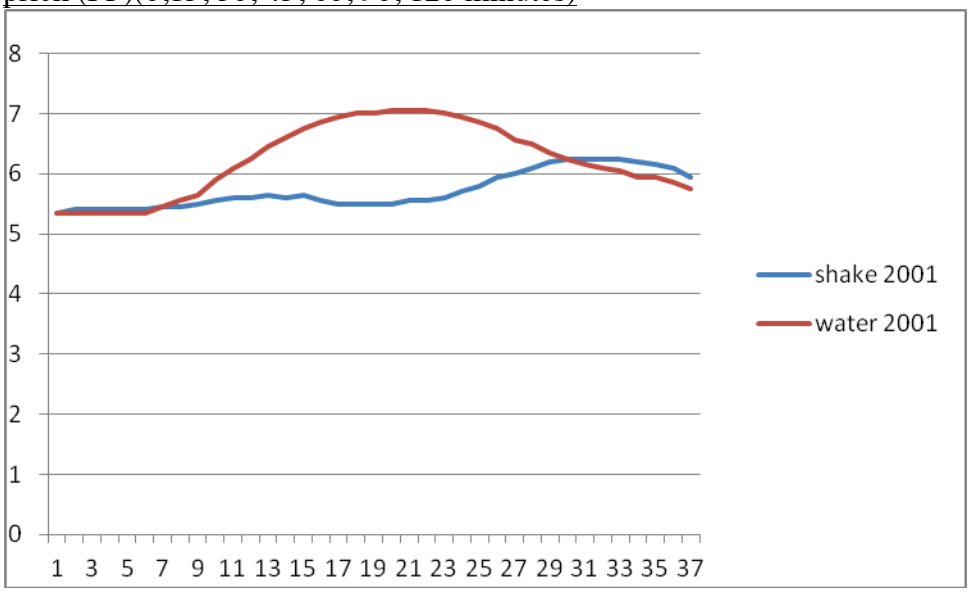
Appendix

Supplementary Figures- individual results for all subjects in phase 2 and 3 (numbers 20xx) and phase 1 (numbers 10xx).

Graphs show glucose in mmol/L with 5 minute values for CGMS and 8 data points for finger prick (FP)(0,15, 30, 45, 60, 90, 120 minutes)



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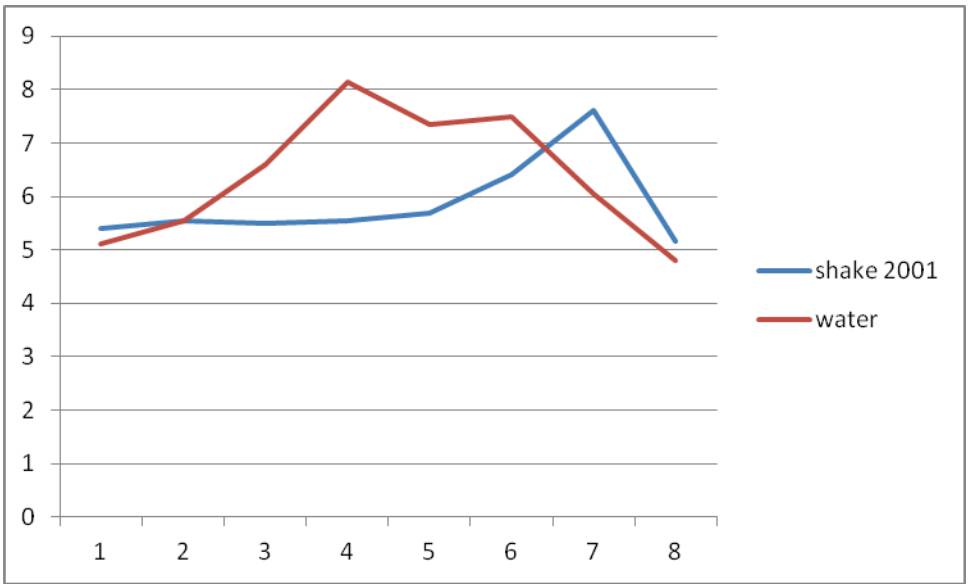
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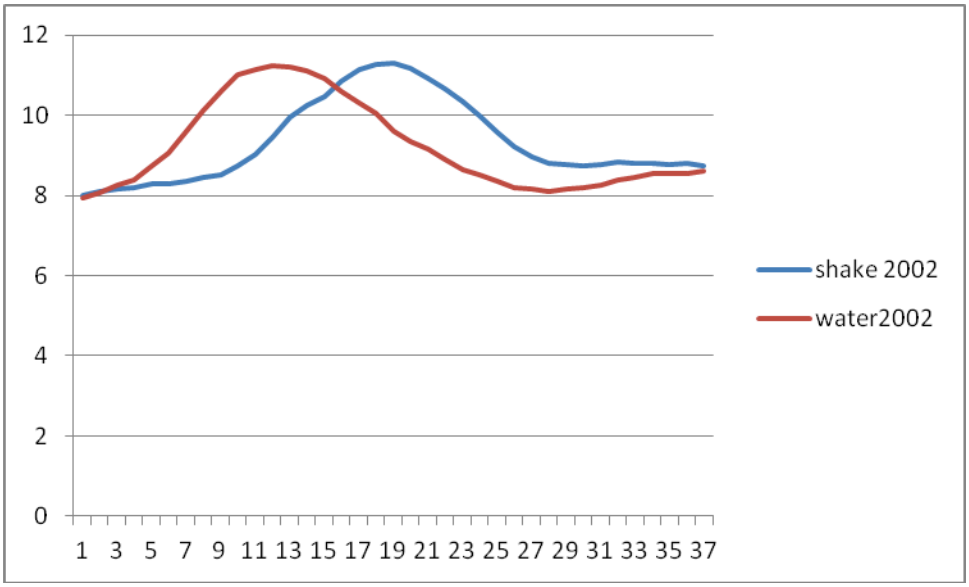
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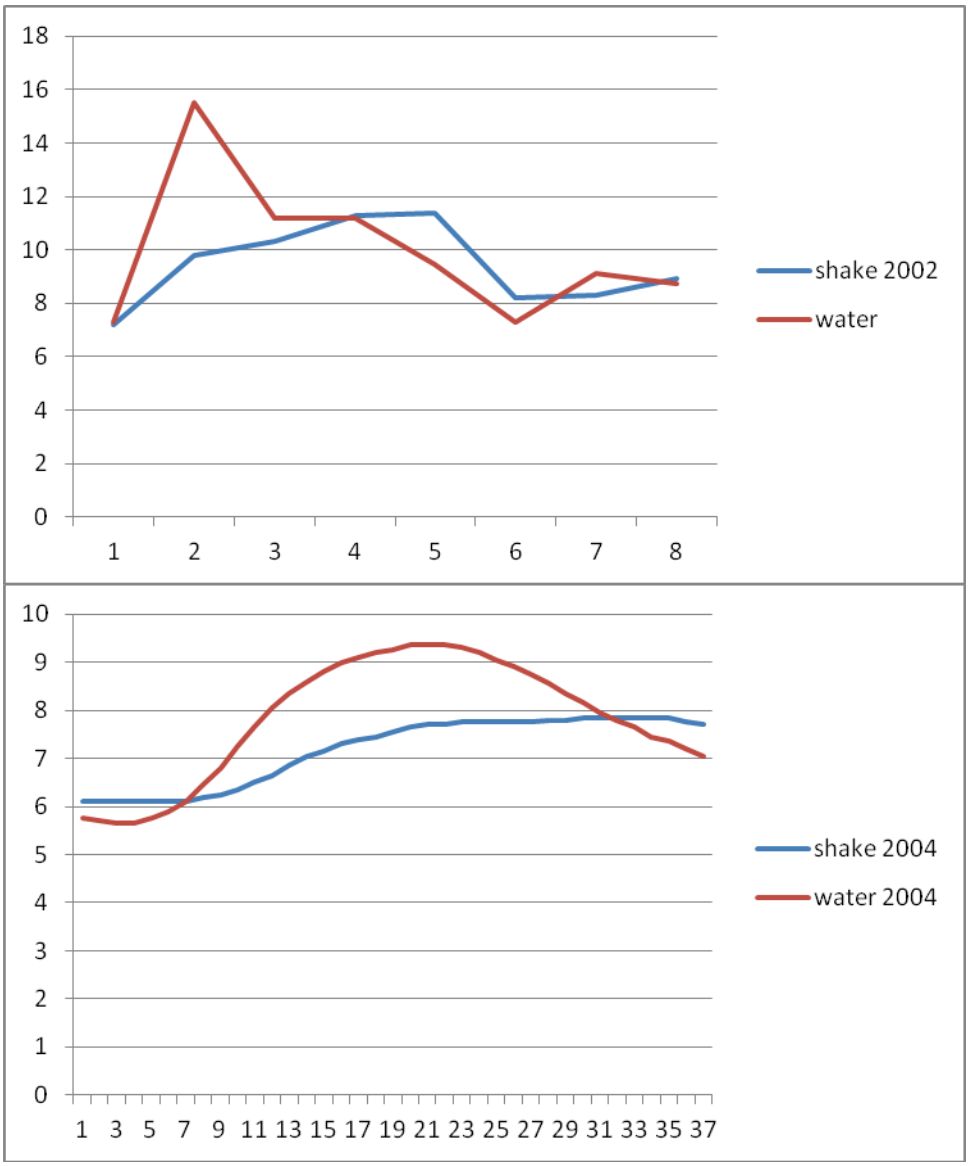
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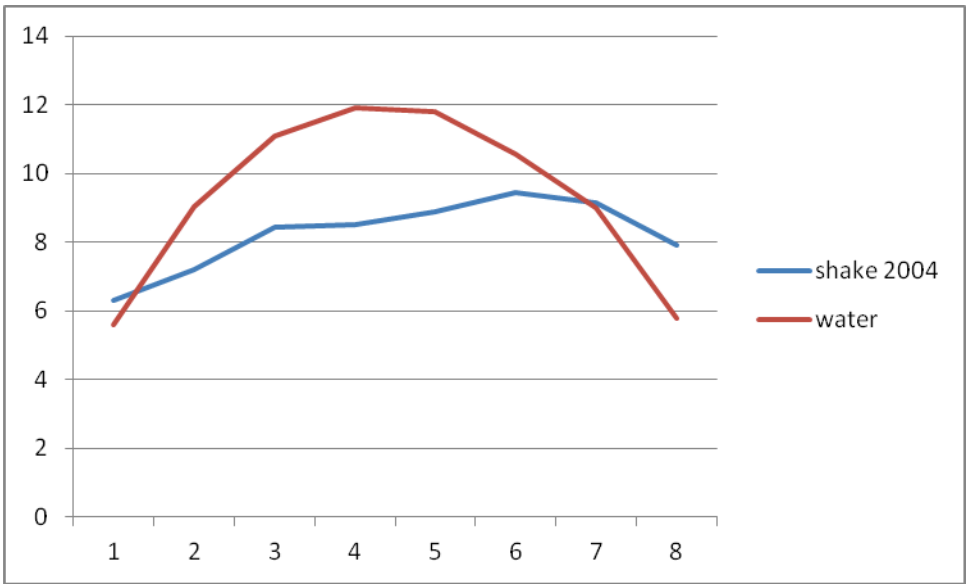
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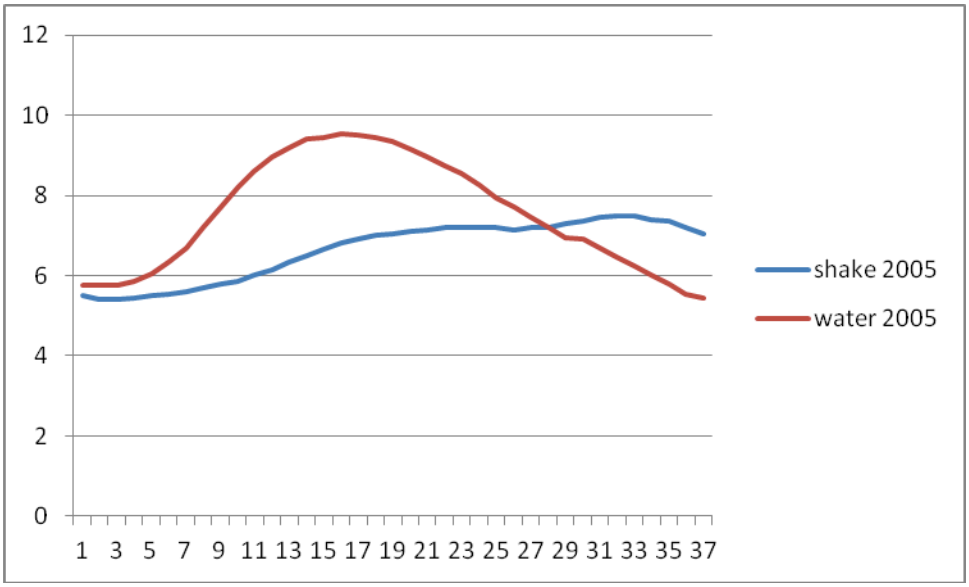
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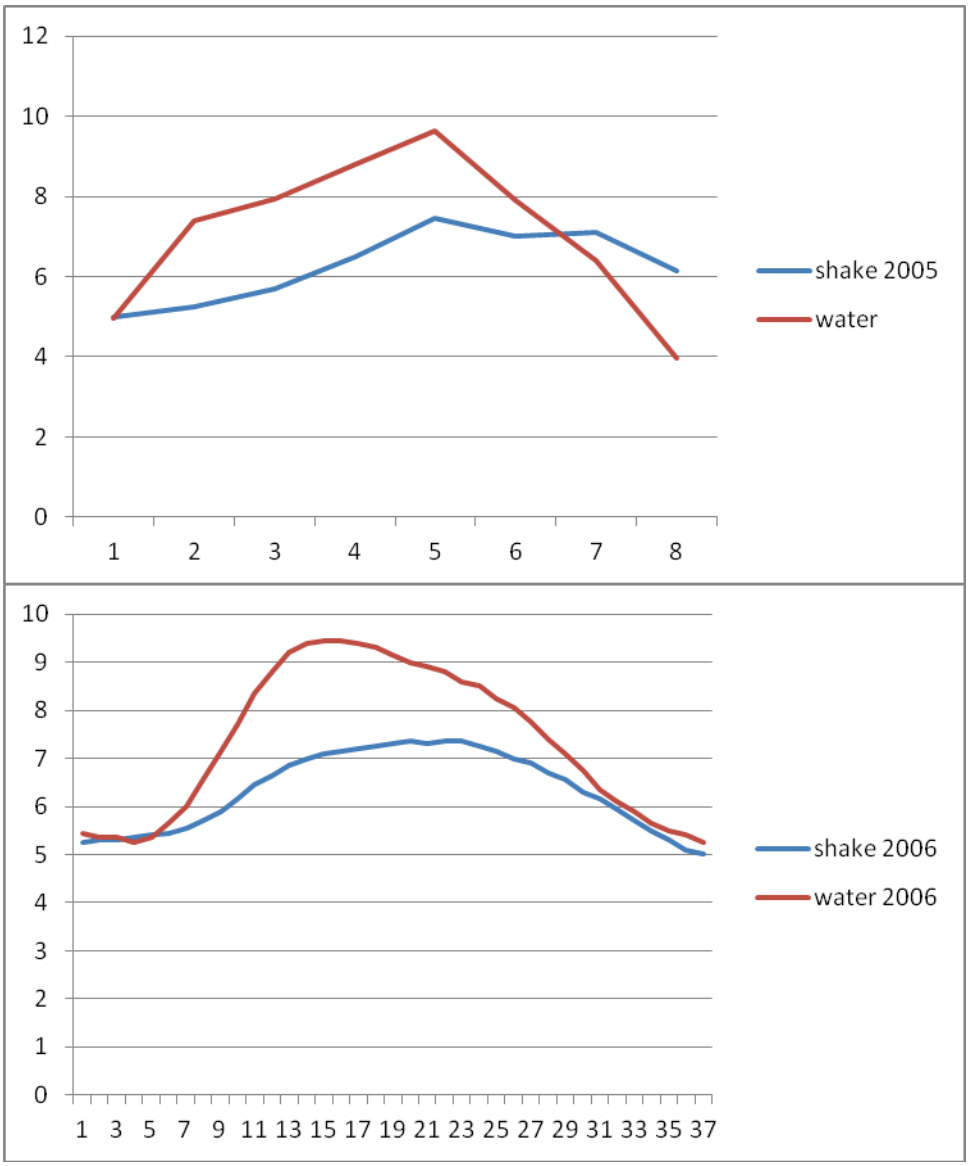
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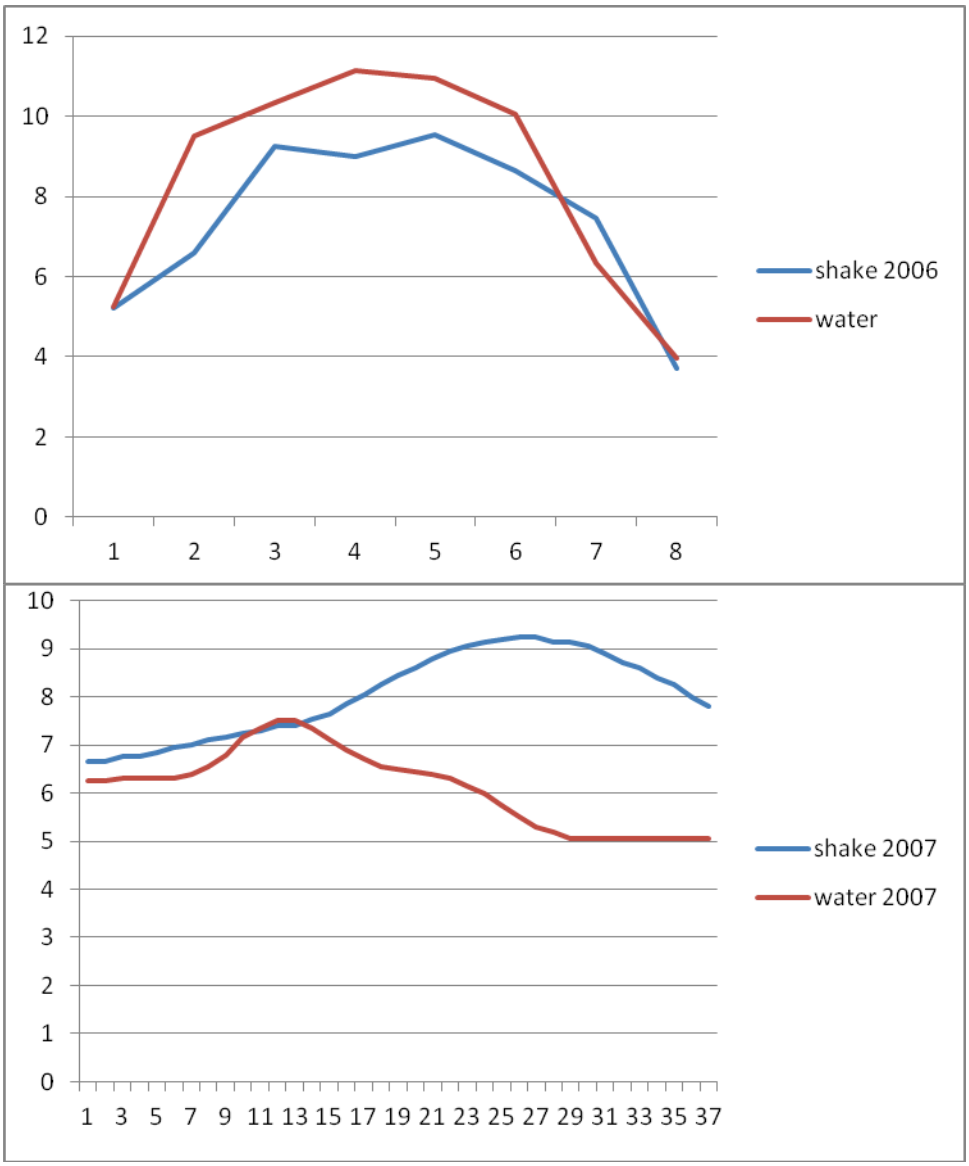
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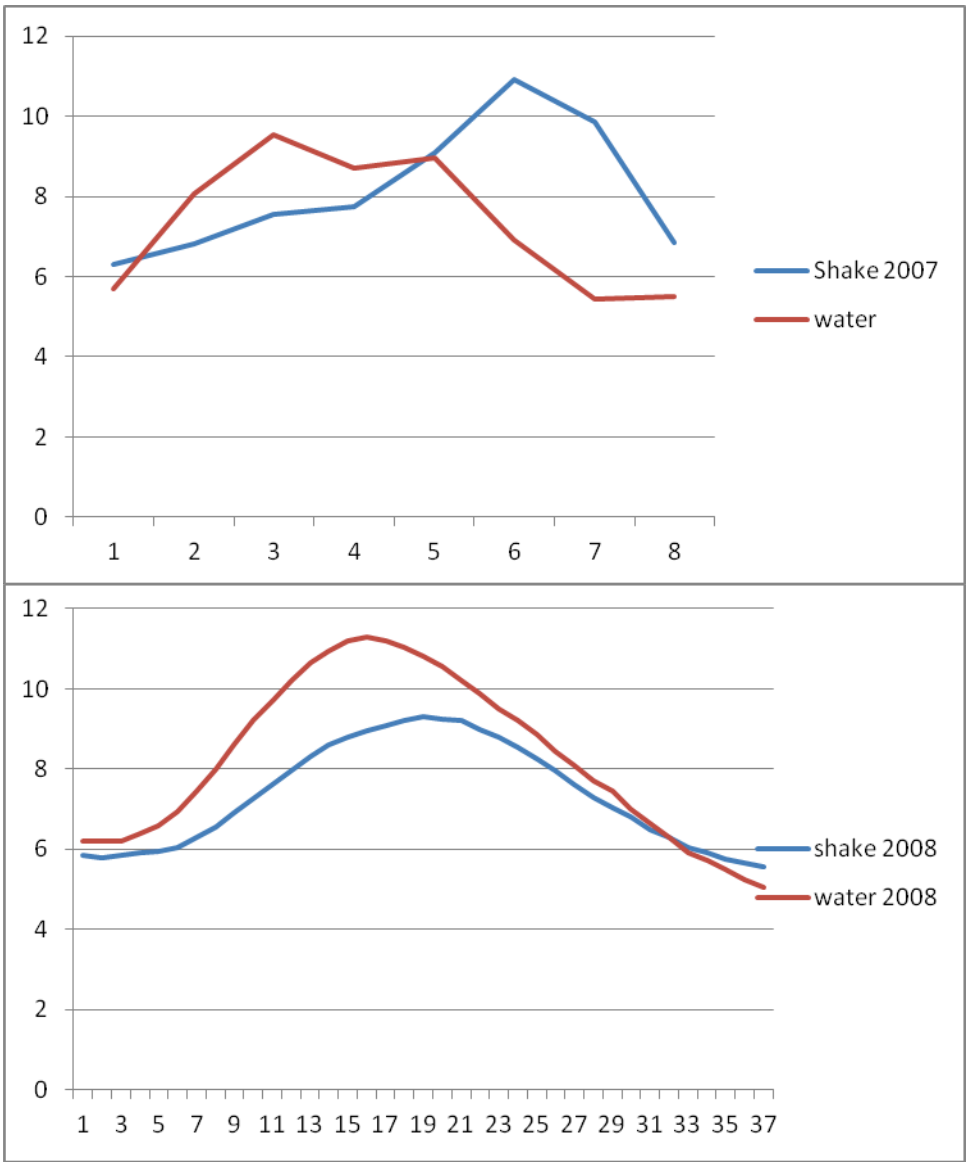
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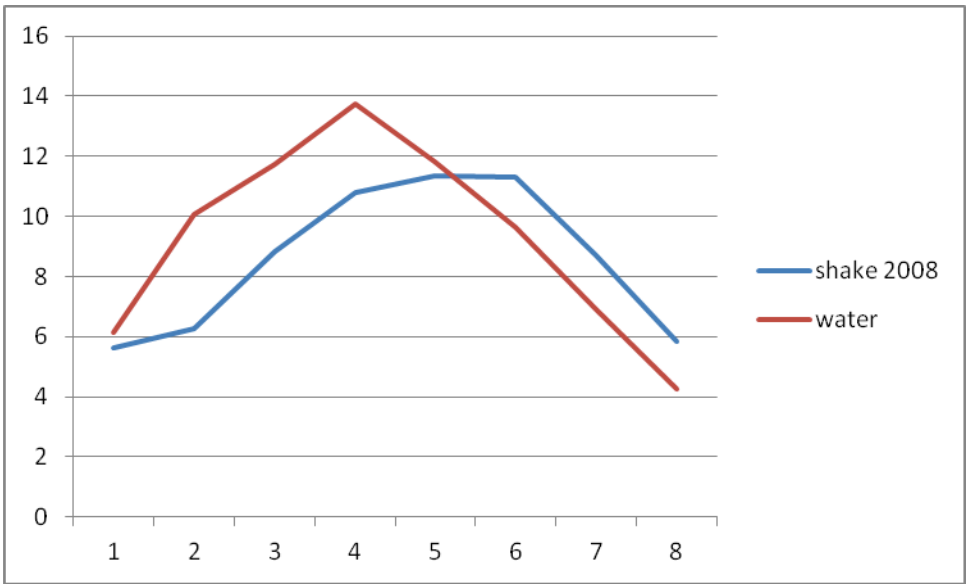
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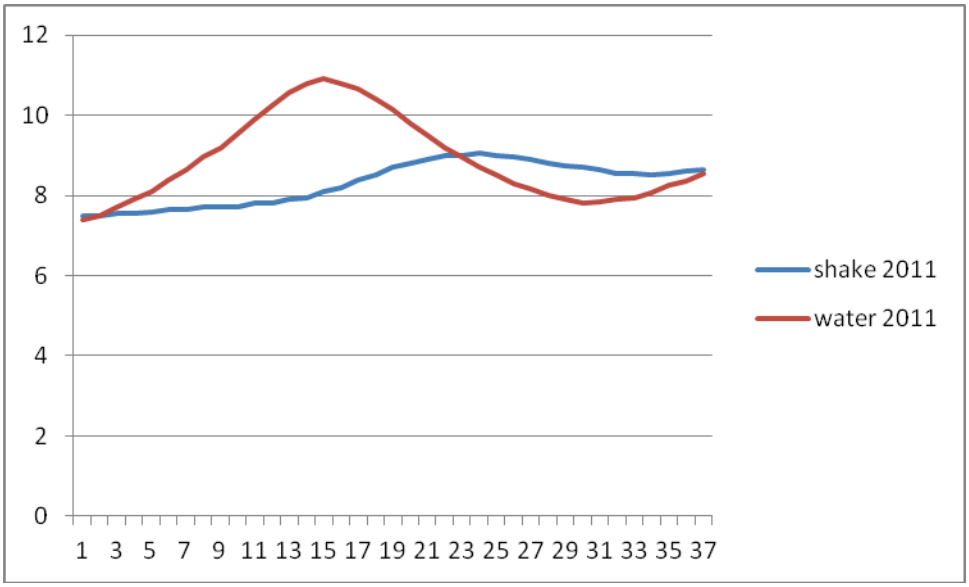
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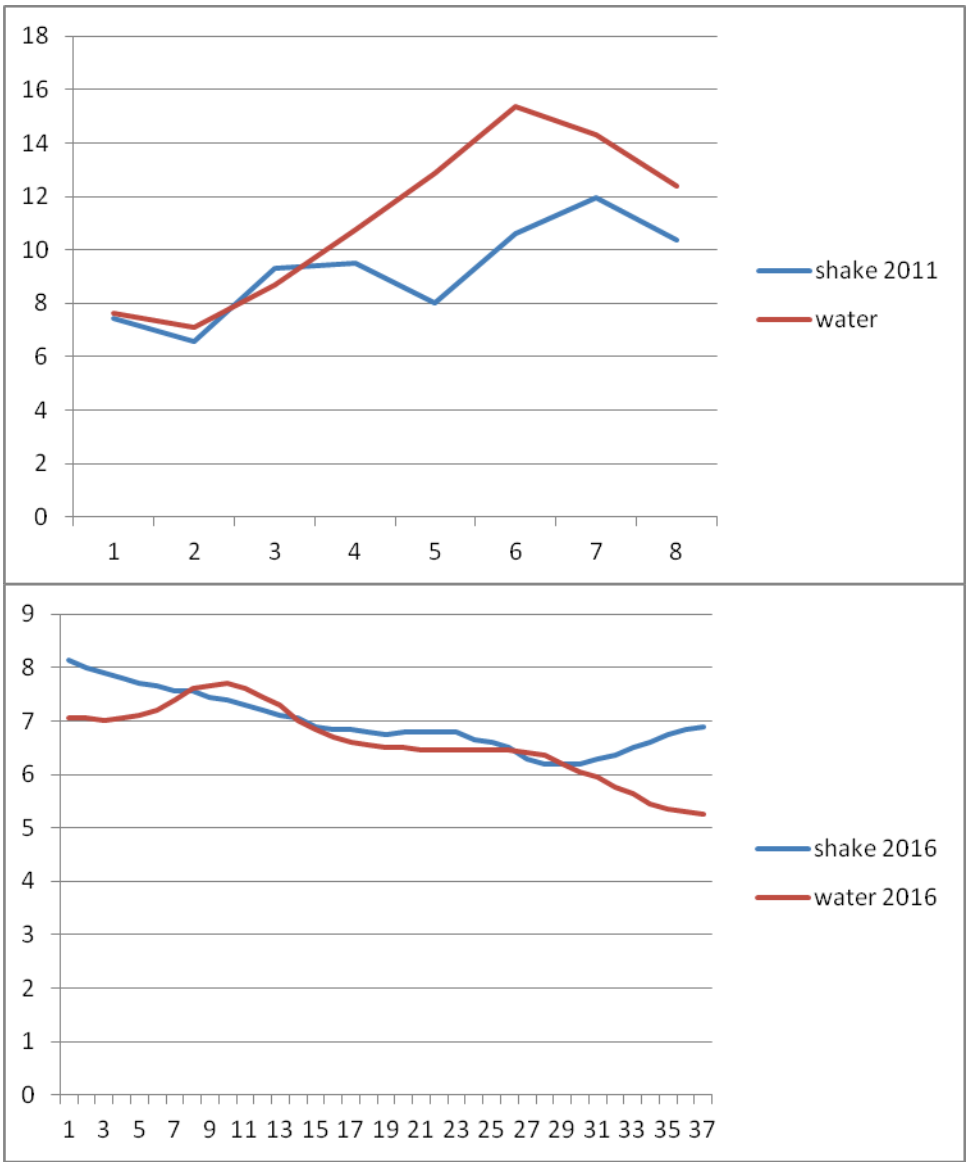
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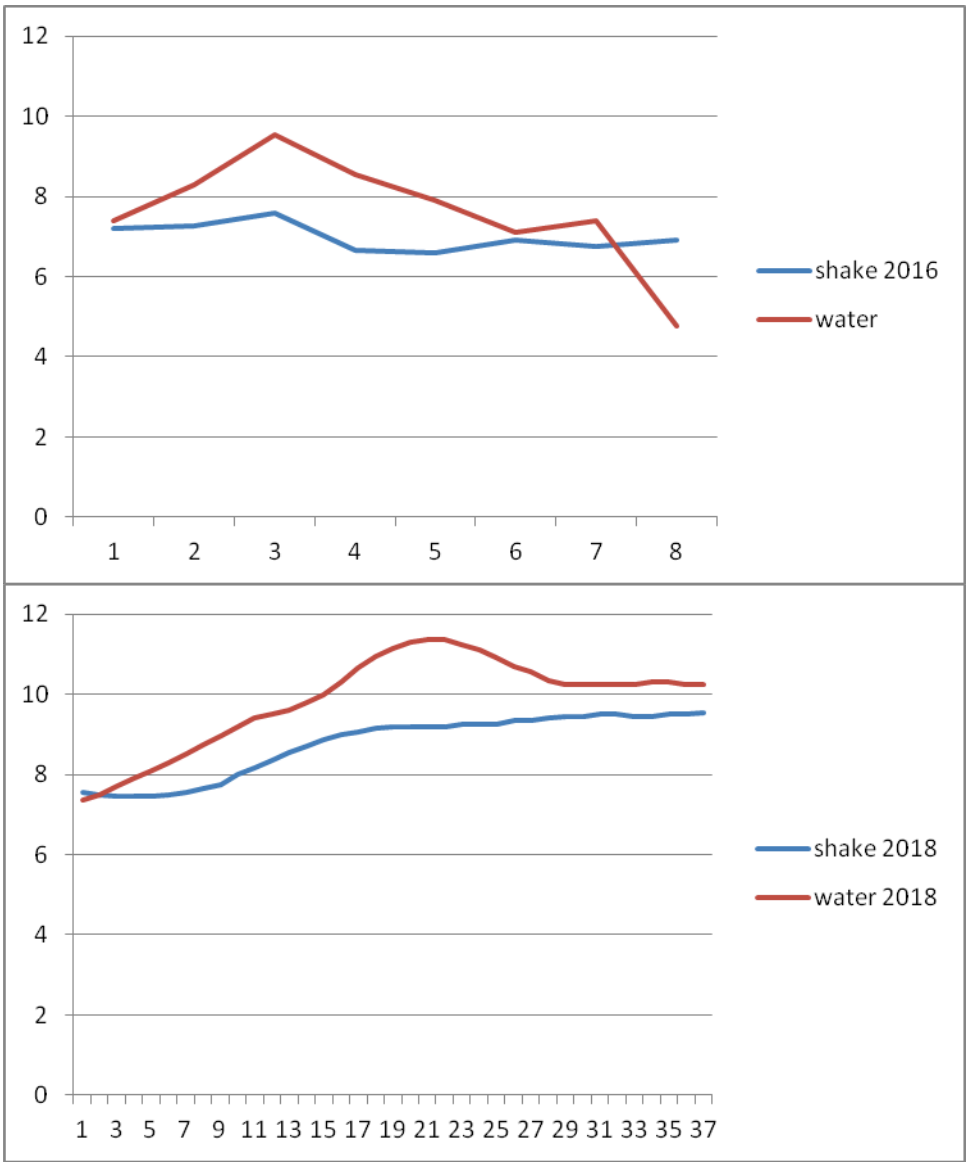
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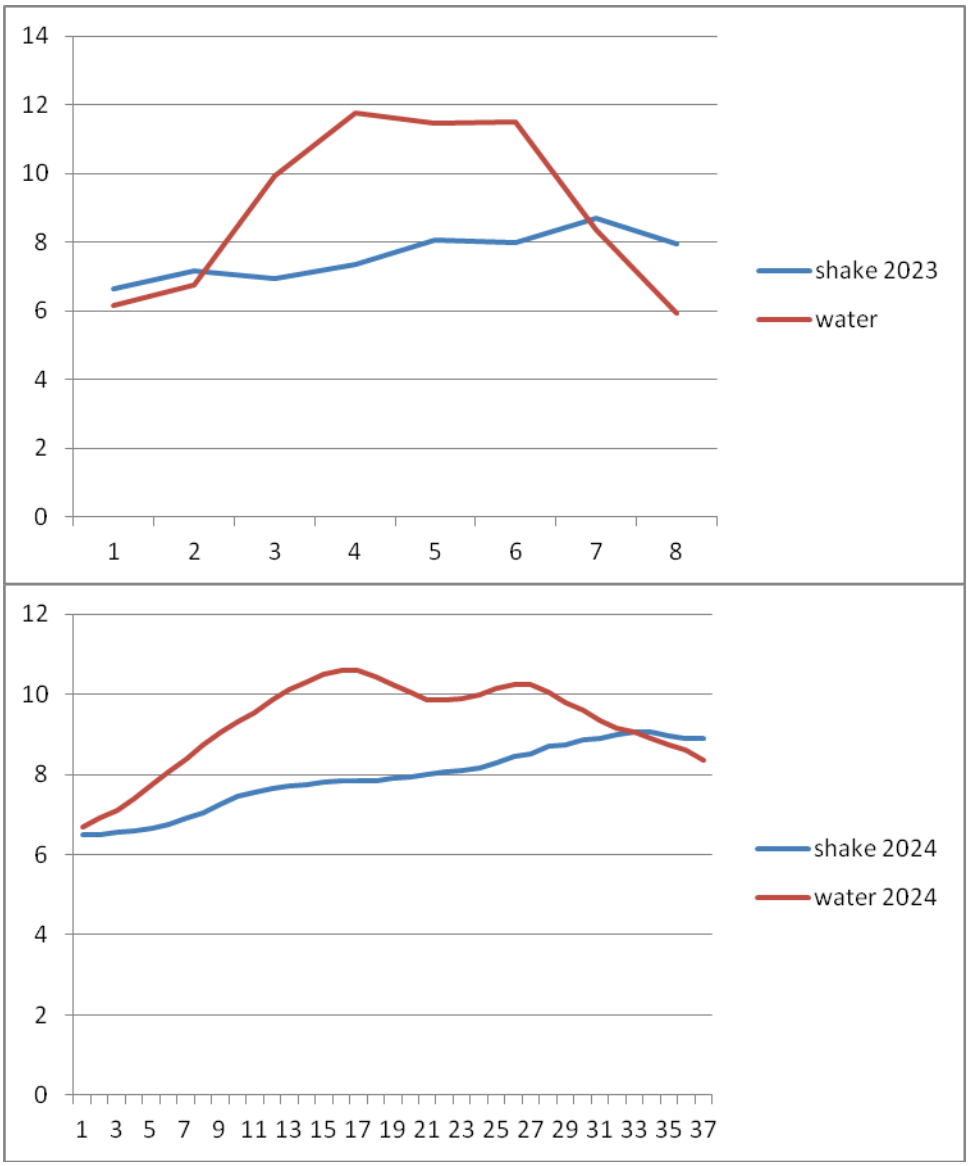
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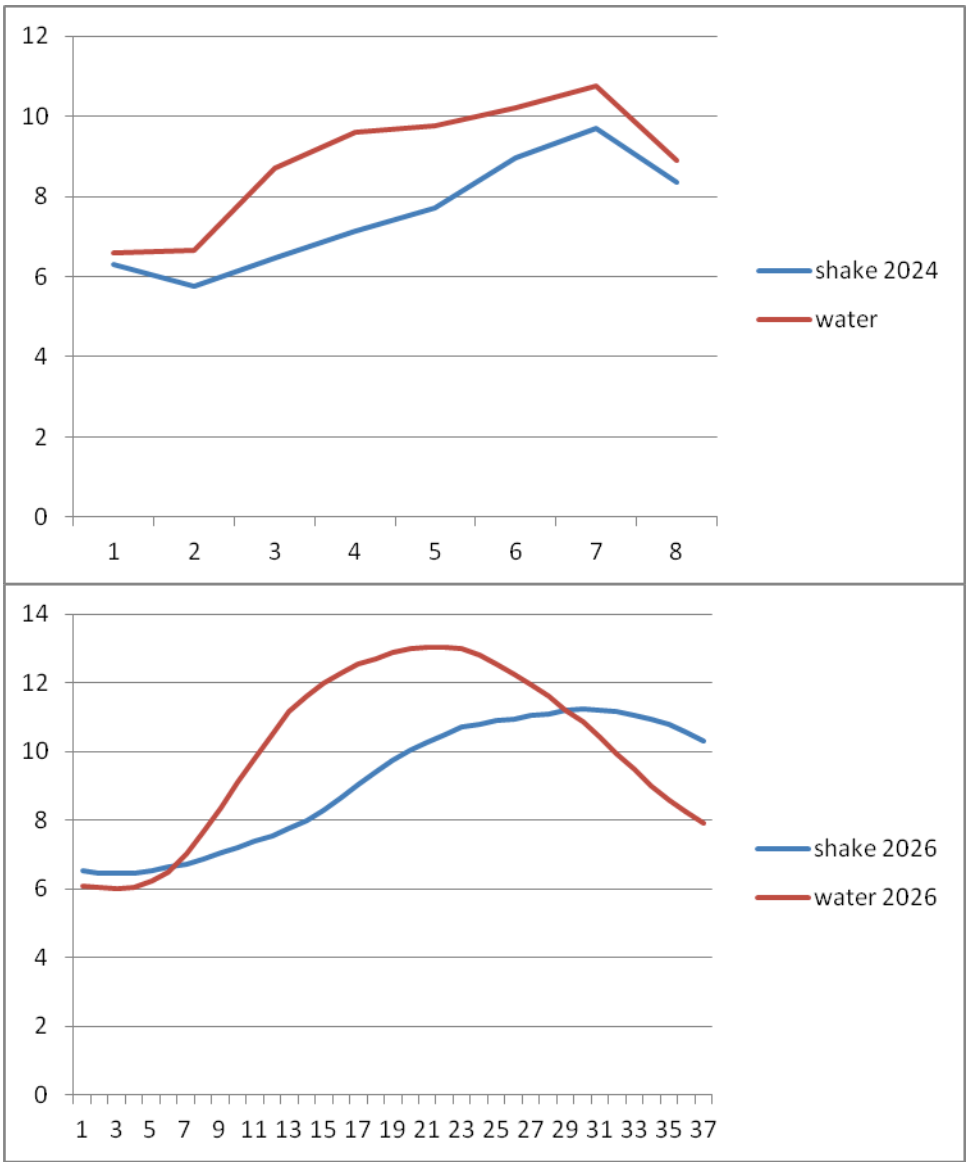
shake 2024
water 2024

FP 2024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shake 2024
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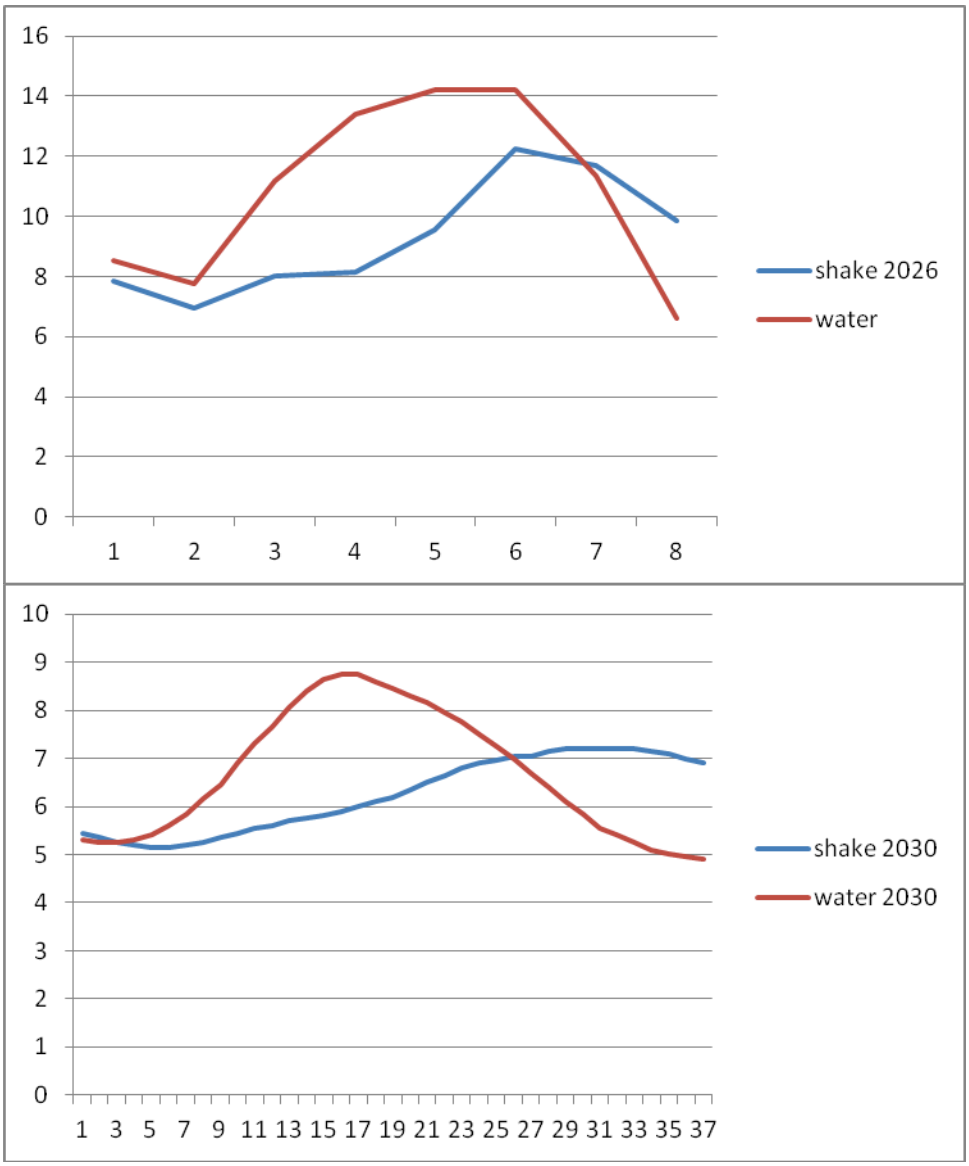
shake 2026
water 2026

FP 2026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shake 2026
water
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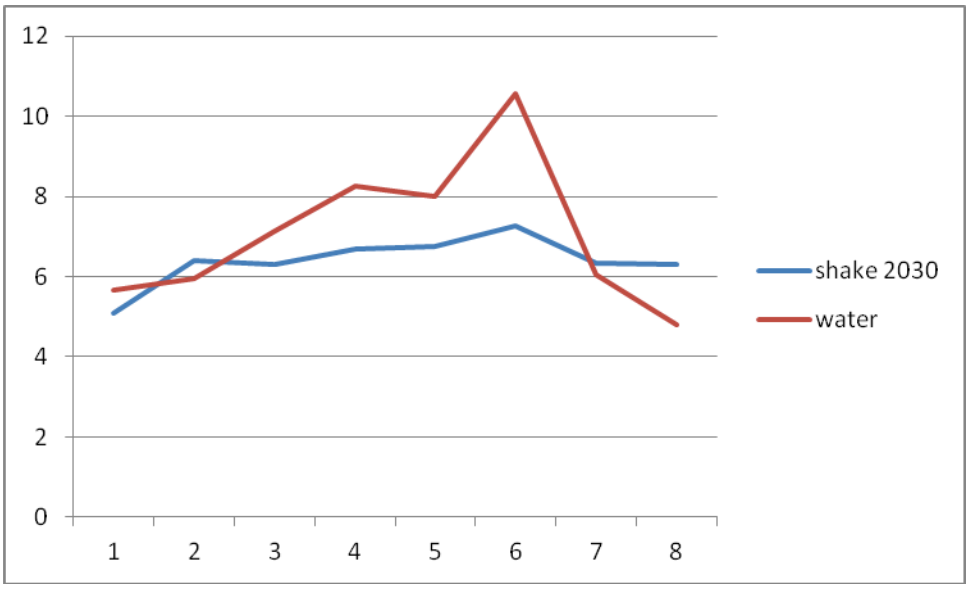
shake 2030
water 2030

FP 2030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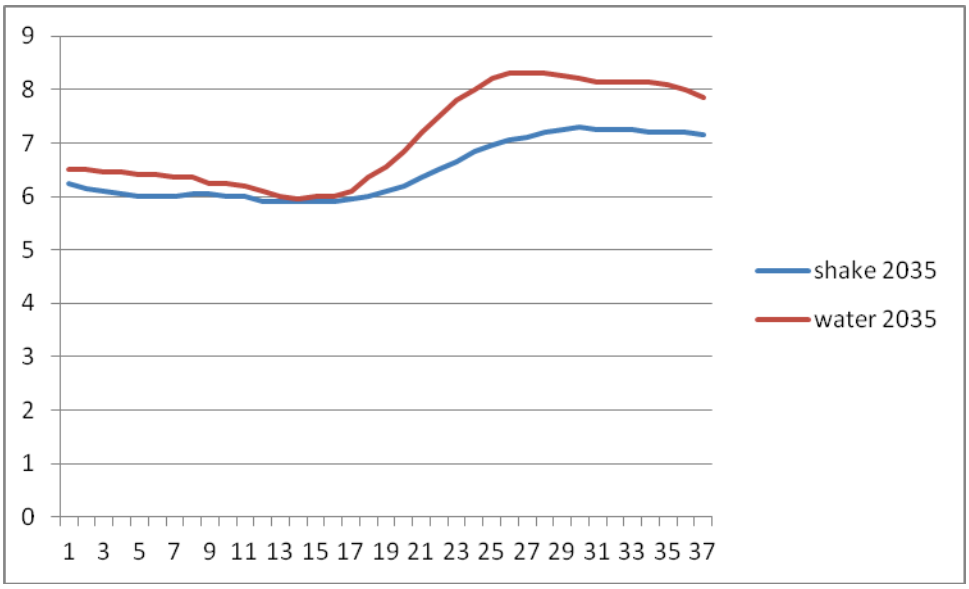
shake 2030
water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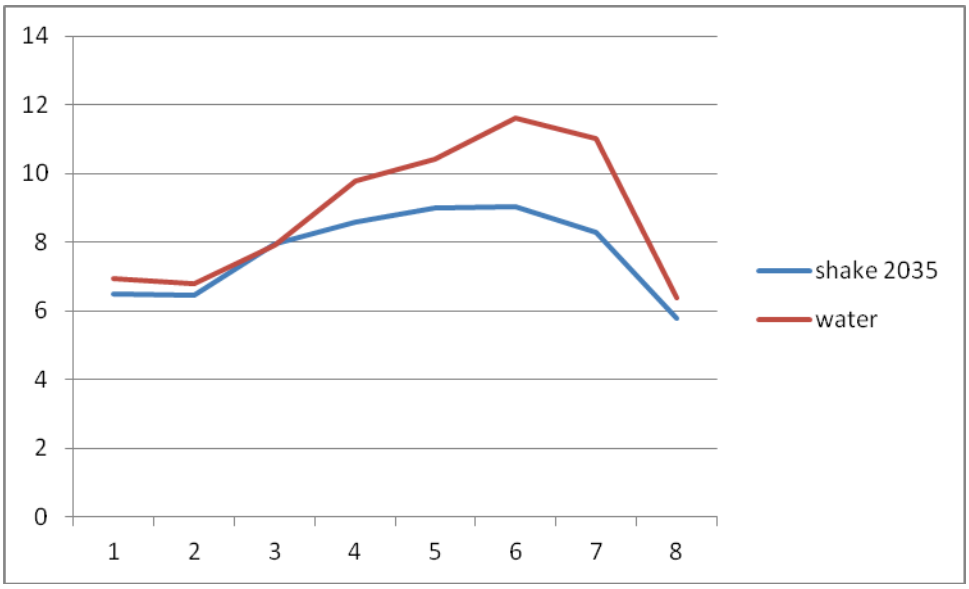
shake 2035
water 2035

FP 2035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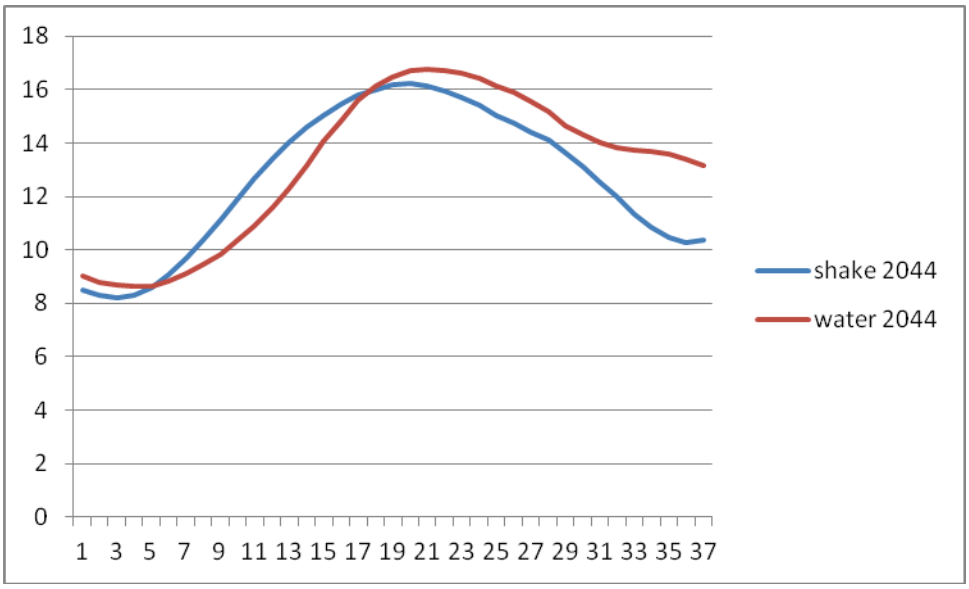
shake 2035
water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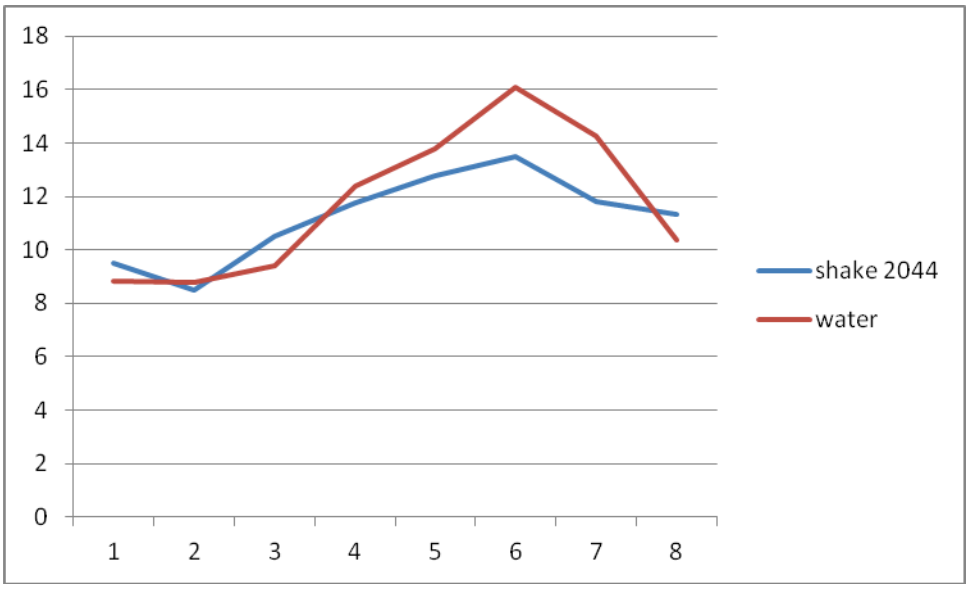
shake 2044
water 2044

FP 2044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shake 2044
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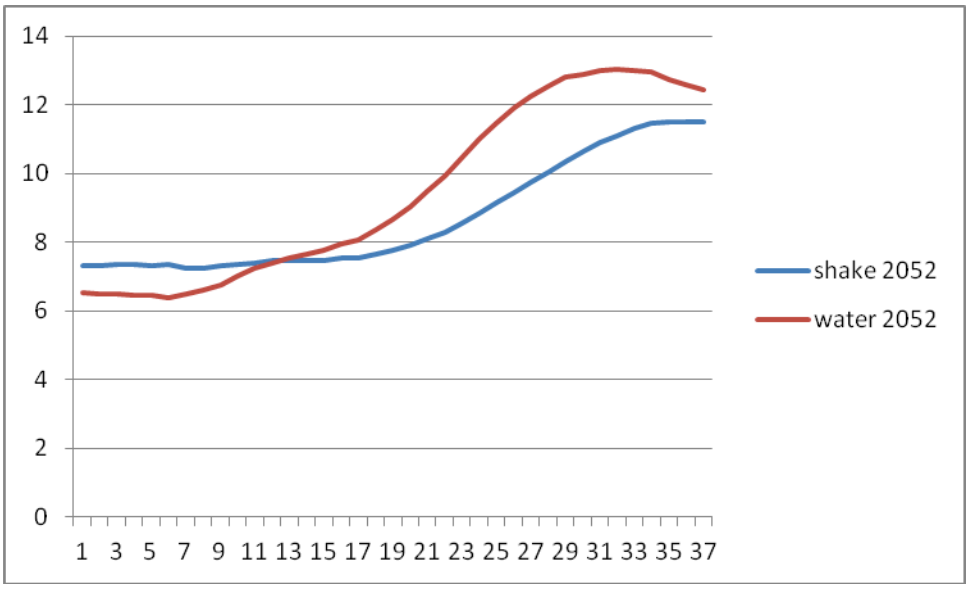
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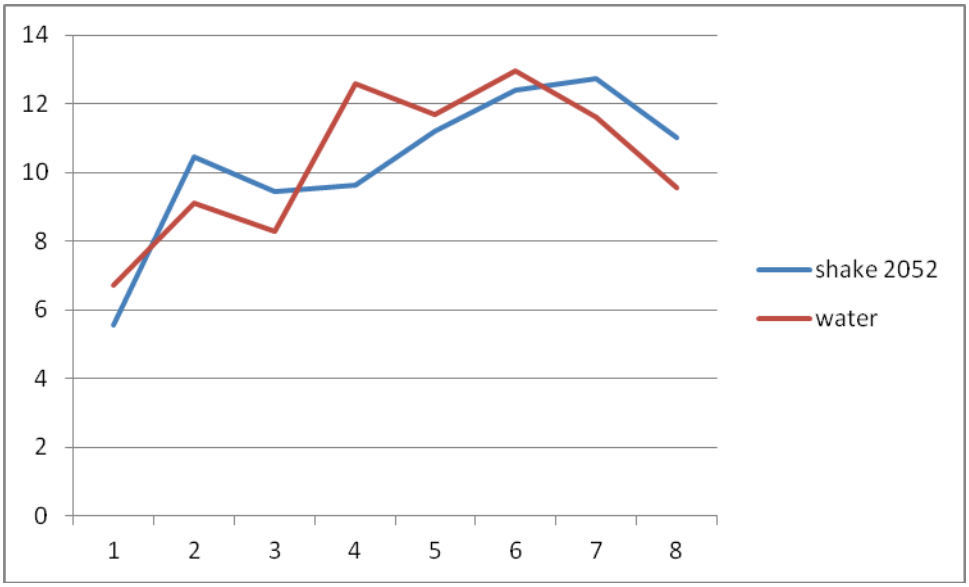
shake 2052
water 2052

FP 2052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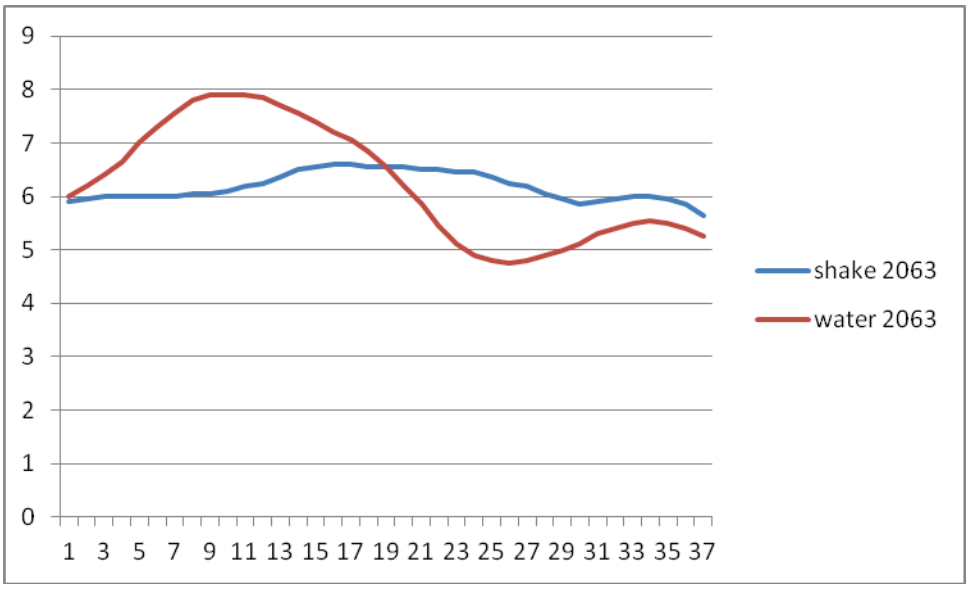
shake 2052
water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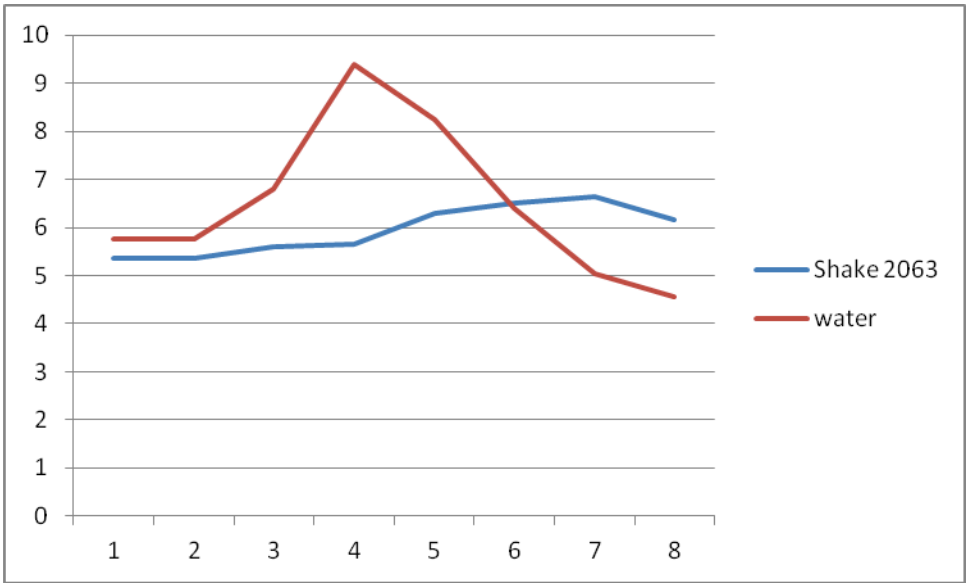
shake 2063
water 2063

FP 2063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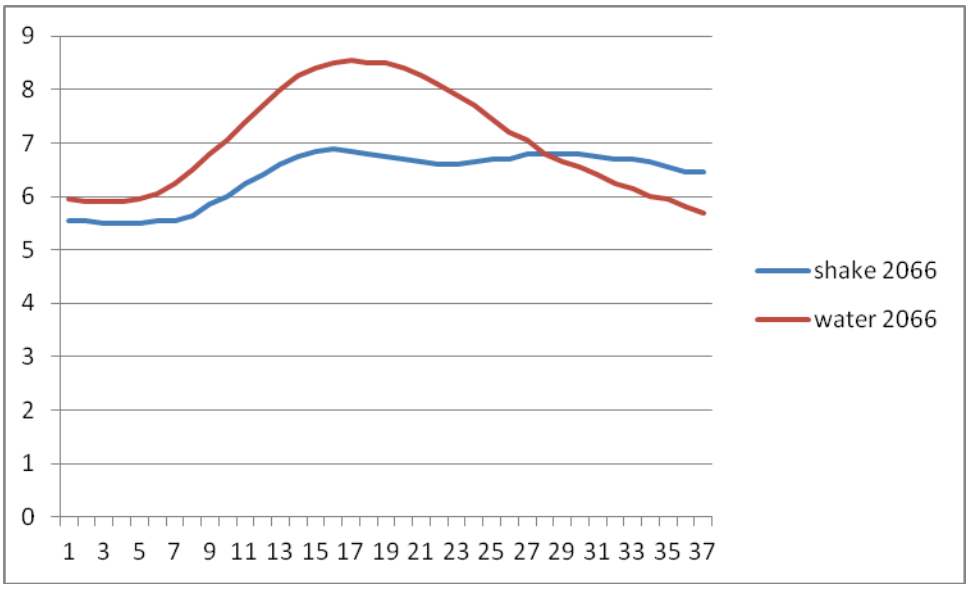
Shake 2063
water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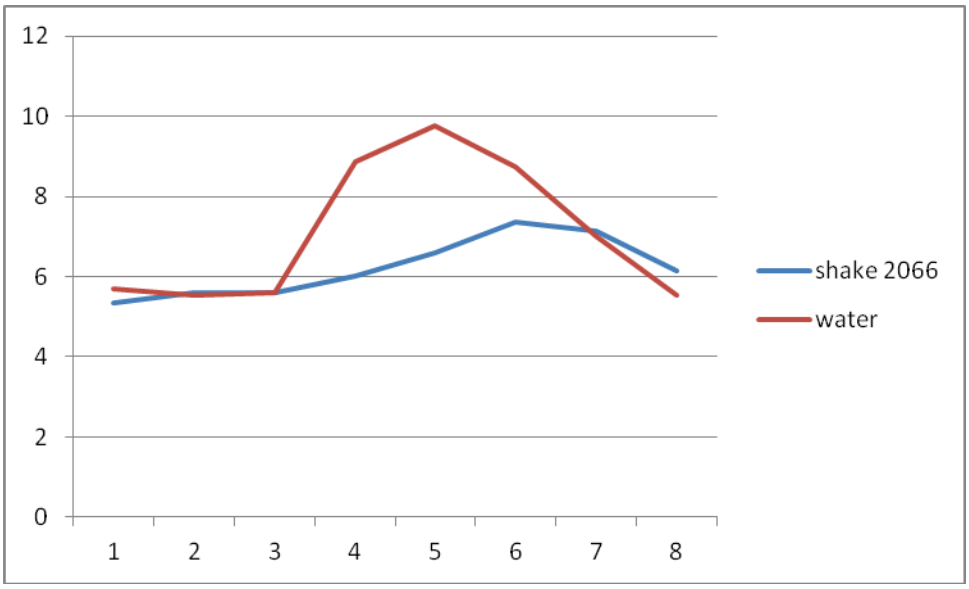
shake 2066
water 2066

FP 2066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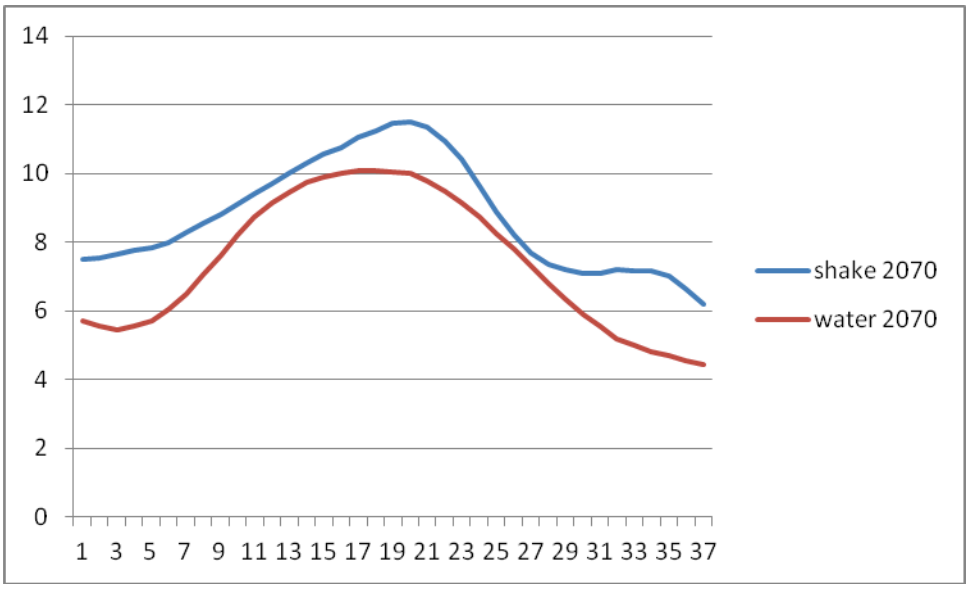
shake 2066
water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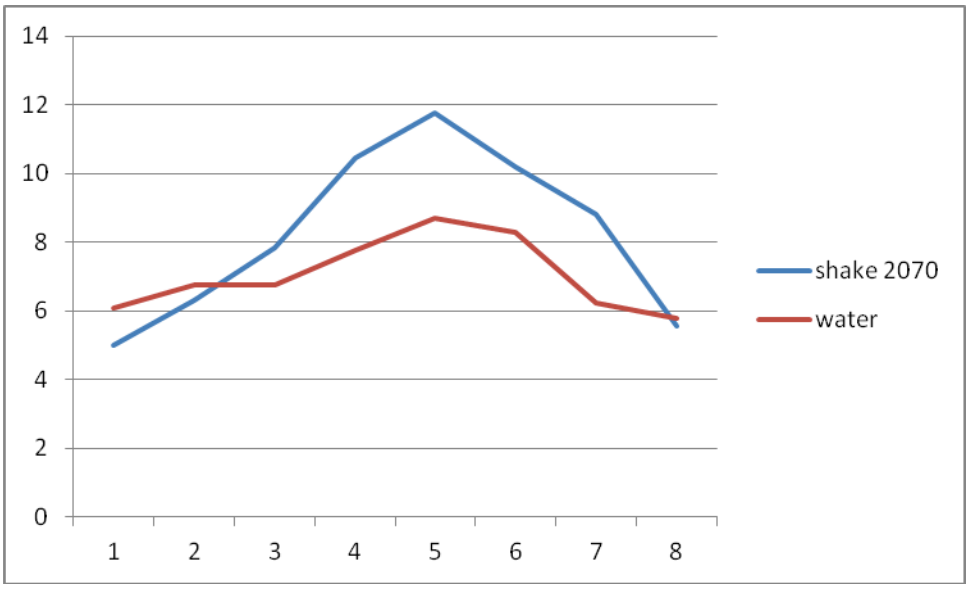
shake 2070
water 2070

FP 2070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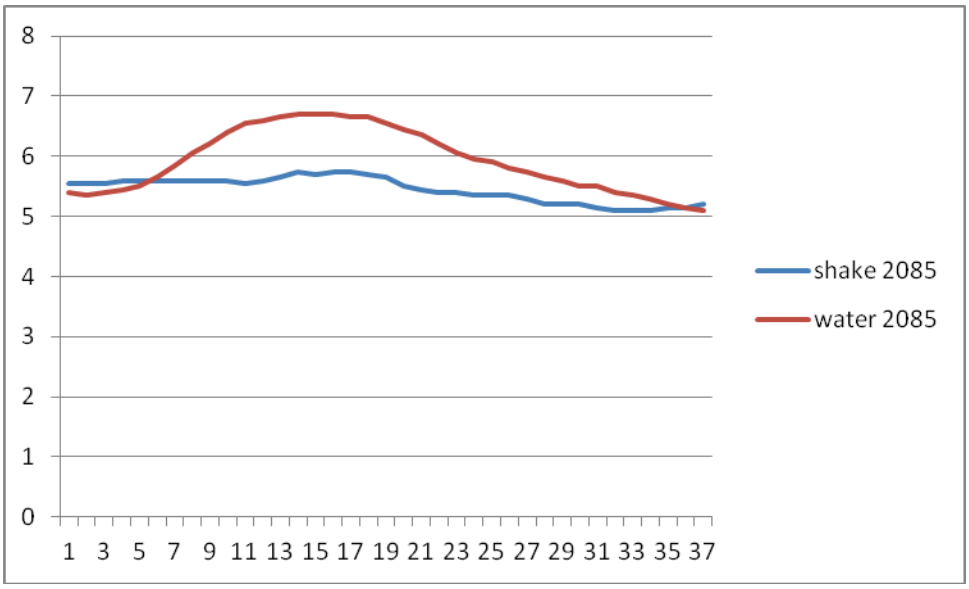
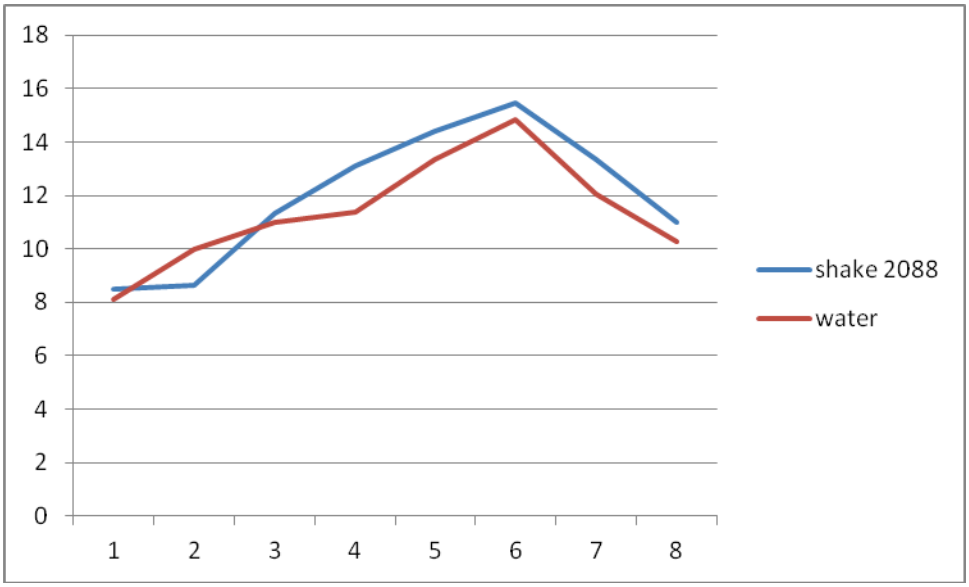
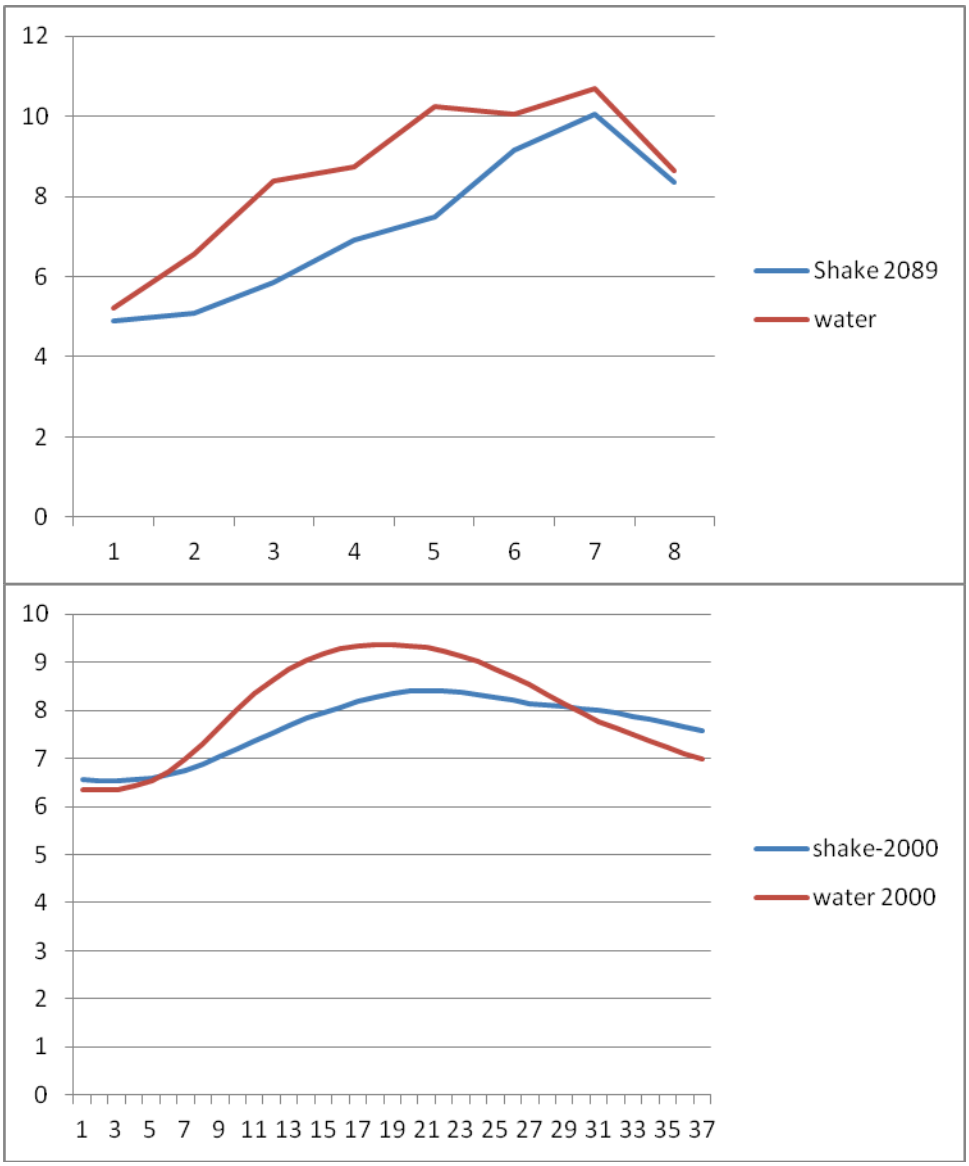
shake 2070
water



FP 2088



FP 2089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8
Shake 2089
water
10
9
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4
3
2
1
0
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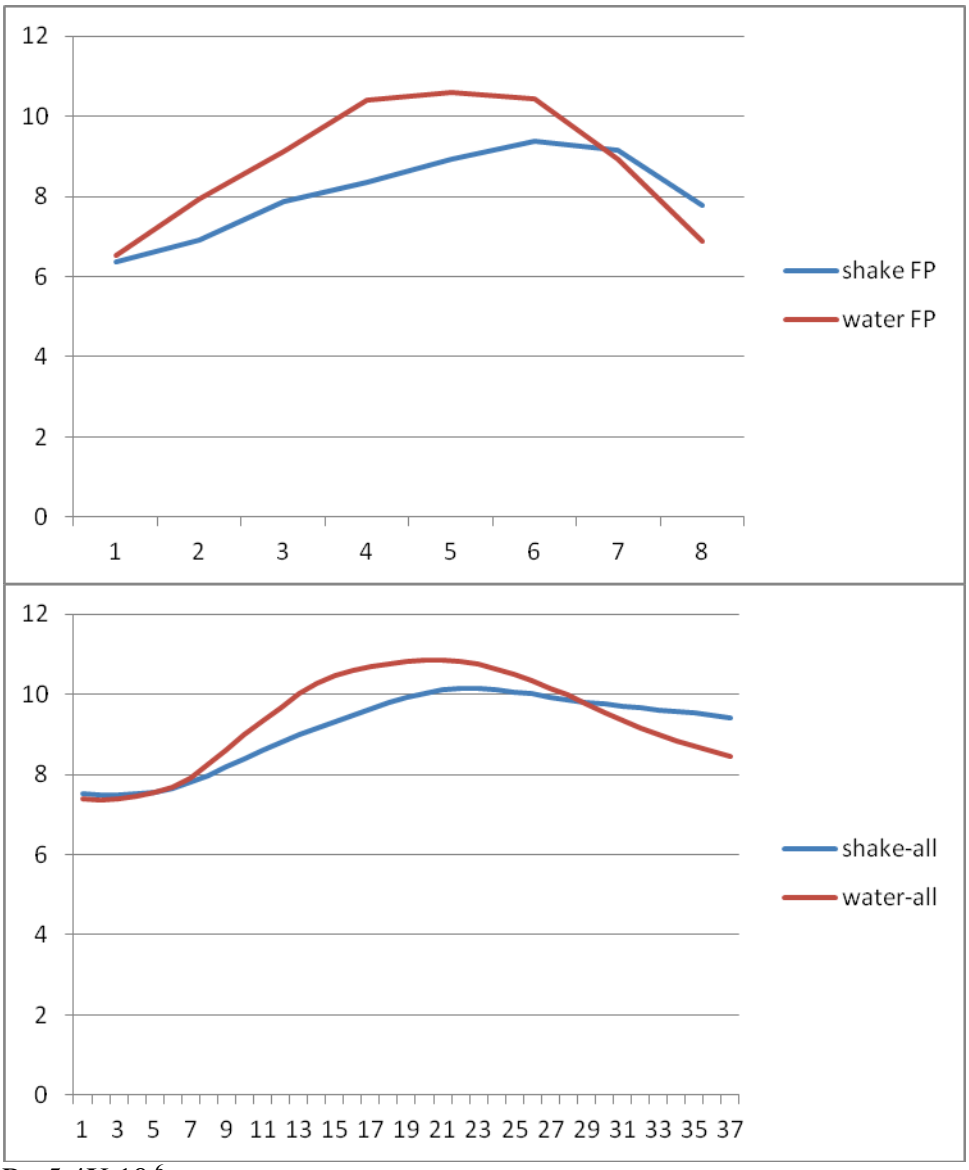
shake-2000
water 2000

FP all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shake FP
water FP
12
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1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37
shake-all
water-all

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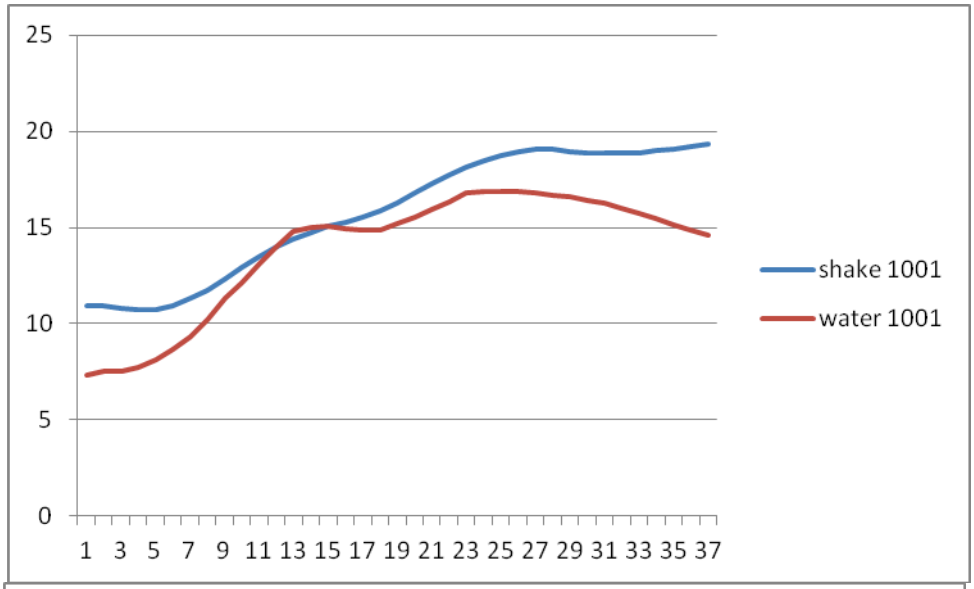
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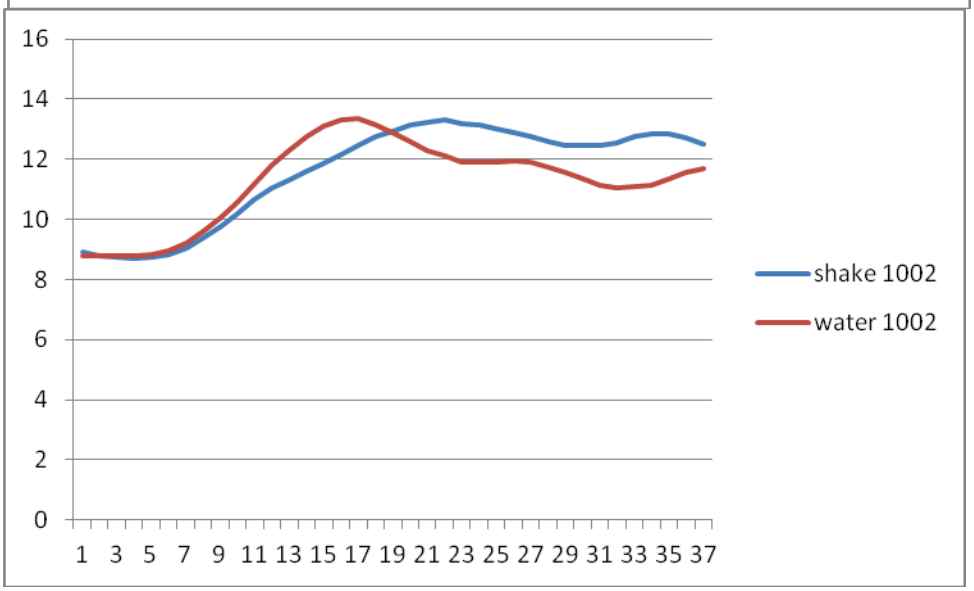
water 1001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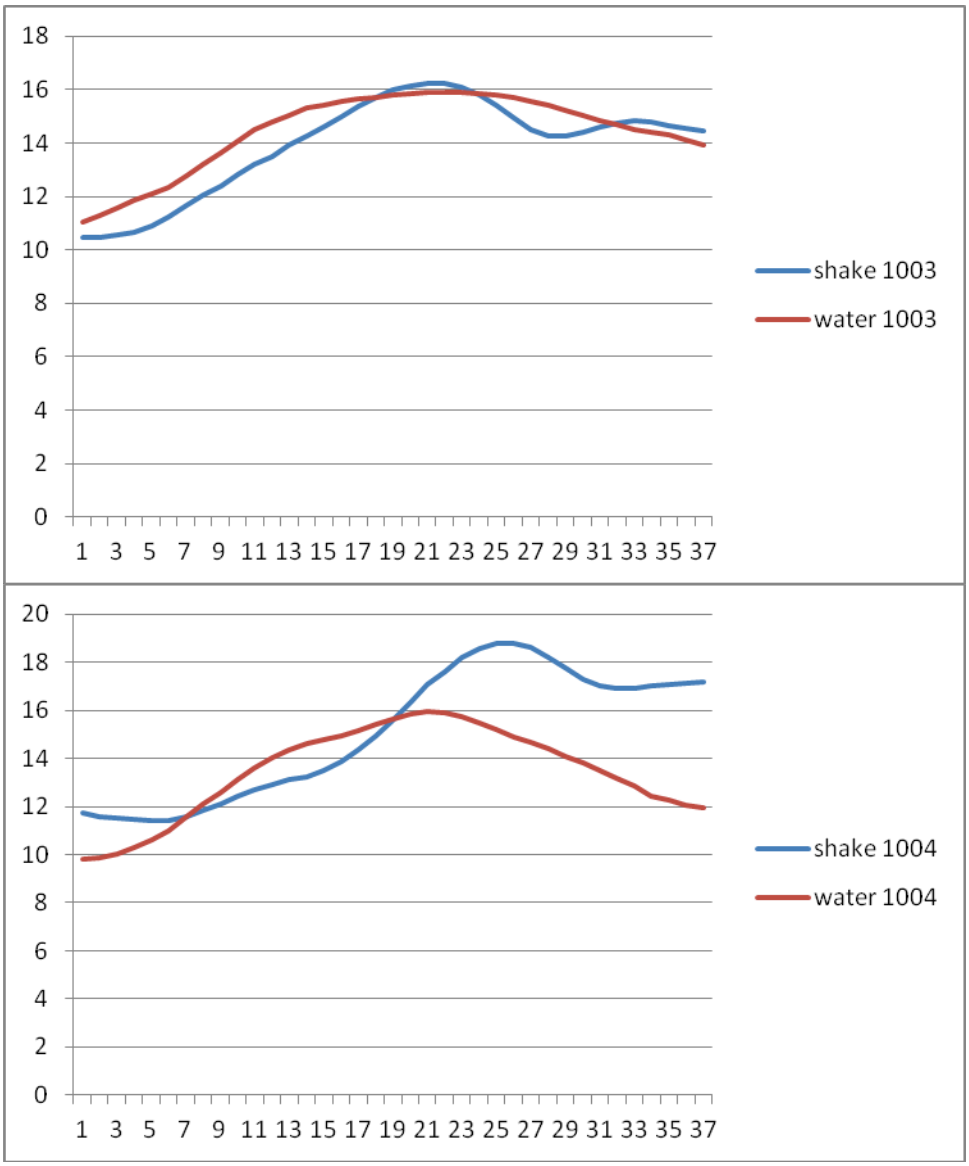
shake 1002
water 1002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shake 1003
water 1003
20
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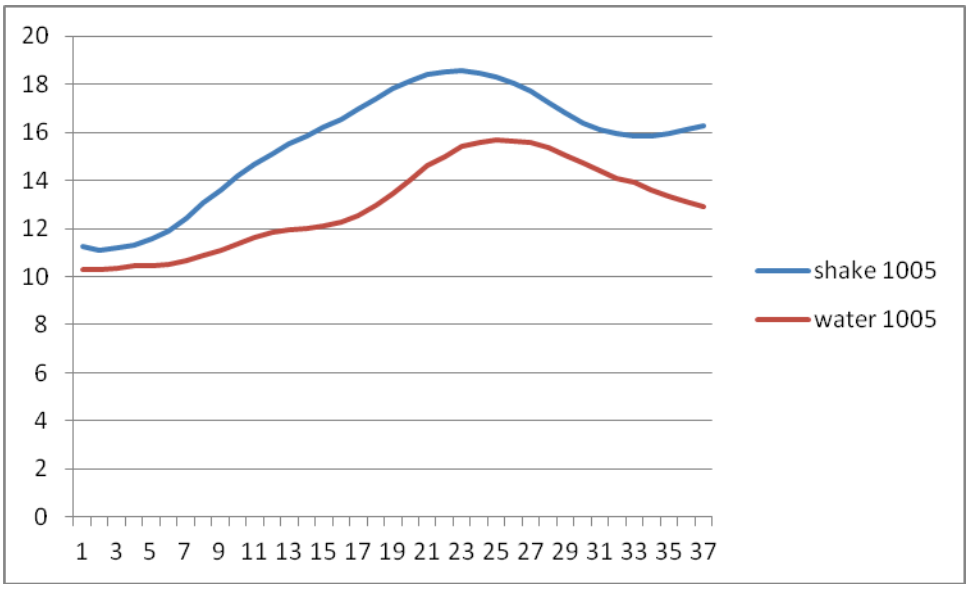
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37
shake 1004
water 1004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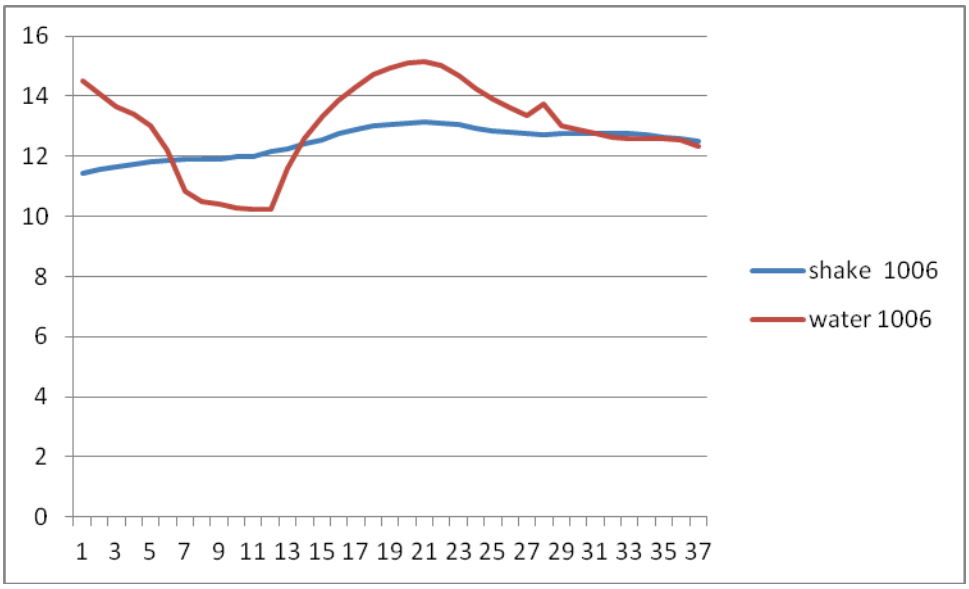
shake 1005
water 1005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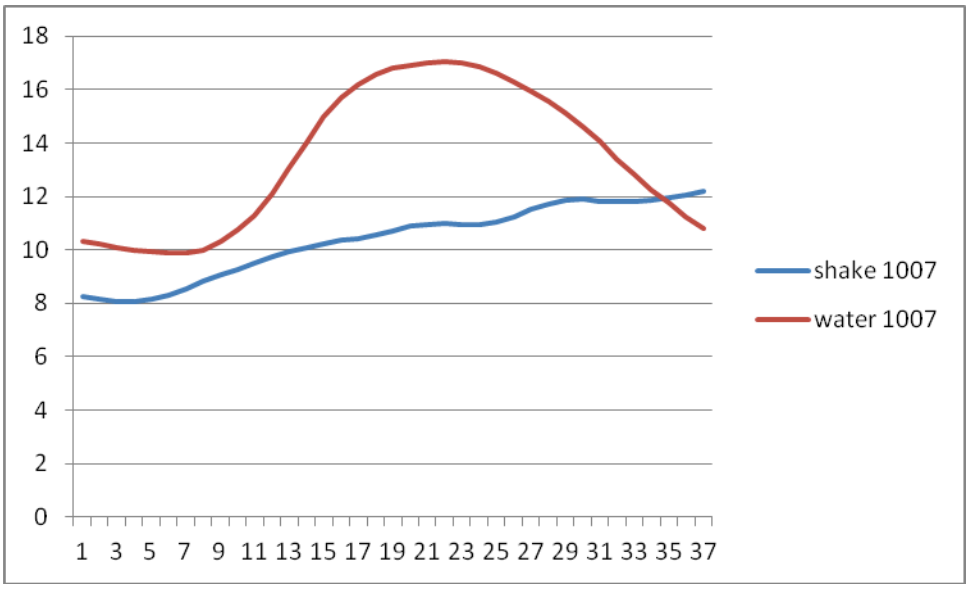
shake 1006
water 1006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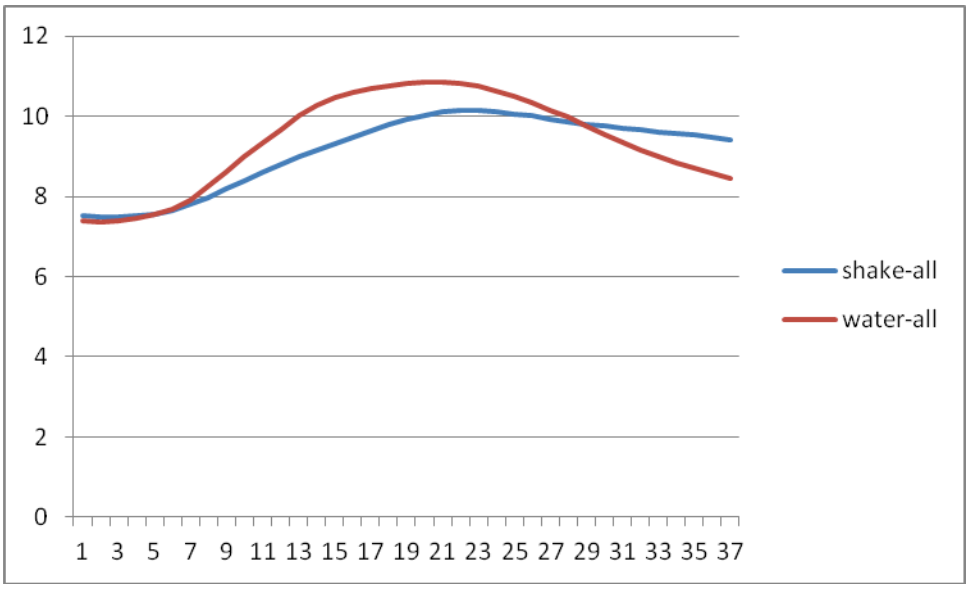
shake 1007
water 1007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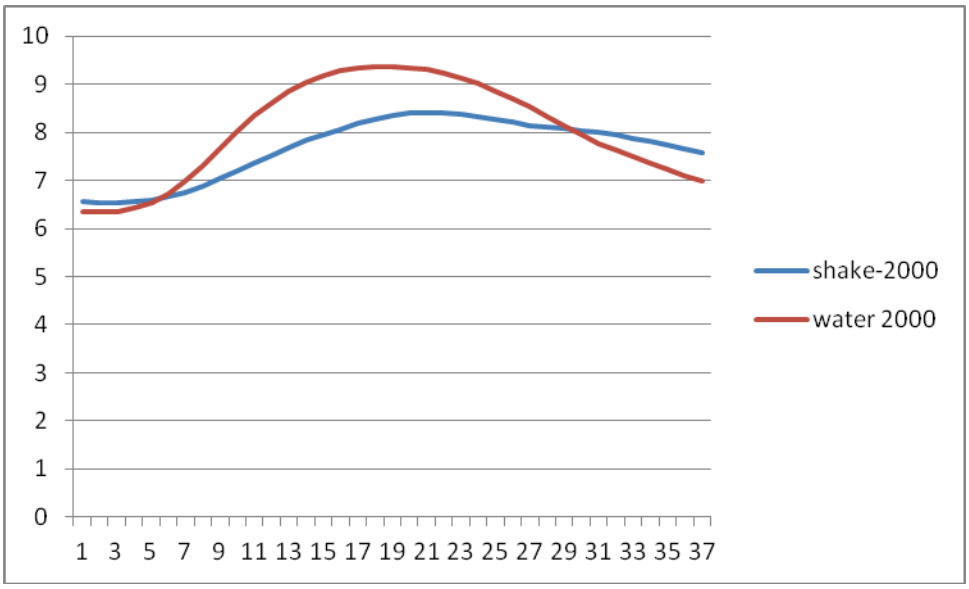
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37
shake-all
water-all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1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37
shake-2000
water 2000