Critically discussing the trends surrounding novel psychoactive substances.

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Masters by Research

Abstract

Novel psychoactive substances (NPS), previously known as ‘legal highs’, have been common in the UK for many years (EMCDDA, 2018). The aim of this research work was to combine spectroscopic analysis with review of literature to assess the trends arising from the use of novel psychoactive substances in the UK.

Handheld Raman Spectroscopy was used to analyse the contents of samples taken from the amnesty bin placed by Avon and Somerset constabulary at the Glastonbury Festival in 2011. These drug samples were then requested by Professor M. David. Osselton for analysis at Bournemouth University in 2011. The novel use of handheld Raman was utilised to test the limitations of the technique. It was also used to give primary information about the type of substances being used during this time. Of all the samples scanned, 48.5% were Raman active; spectra were yielded for all the Raman active substances.

A review of the literature took place, with the use of Boolean operators to systematically search for contemporaneous literature. The use of key words, such as ‘novel’, ‘psychoactive’, ‘substances’, with defining key words such as, ‘prevalence’, ‘use’, to refine the articles for inclusion. By reviewing the literature it showed the need for intervention, how the government primarily responded and then how this finally culminated in the Psychoactive Substances Act 2016.

With a combination of sciences and methods it has allowed for the critical discussion of the trends surrounding NPS and this thesis is the culmination of this work.

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Introduction

Novel psychoactive substances (NPS) have been under review for the past decade and longer. Within the European Union, the early-warning system has been in place since 2007, to monitor the prevalence of NPS from drug seizures within member states (European Monitoring Centre for Drugs and Drug Addiction, 2007). The early-warning system is inclusive of all member states to submit when seized, any new psychoactive substance after toxicological testing. By submission, these samples would then be reviewed by the joint European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)-Europol commission. After the early-warning system was implemented, the number of seizures and NPS coming to the market has been tracked and has been ever-rising since then (EMCDDA, 2018). In the UK, the problem peaked in severity when the deaths had nearly doubled from 2012 to 2013 from NPS usage (Office for National Statistics, 2013). In December 2013, the UK Government convened an expert panel on NPS, where their recommendations were amongst many, to ban NPS (Panel, 2014). This came to fruition in 2016, whereby the Psychoactive Substances Act became enforced across the UK. It banned the production, importation and the supplying of substances, which are 'capable of producing a psychoactive effect in a person who consumes it' (Psychoactive Substances Act, 2016, Ch. 2, s1, ss. a). Exemptions were made for medicaments, foods or foods used for physiological benefit, so the caffeine in coffee, food supplements such as turmeric capsules, or the nicotine in tobacco were exempt from the Act. Further discussion into substances and the associated psychoactive effect takes place in section 5.

Defining NPS is also key during this research. With the media calling NPS, "legal highs" (BBC, 2018), (The Telegraph, 2018), this brings about the notion that because something is legal it is therefore, safe (Sheridan, 2010).

To limit confusion, Novel Psychoactive Substance will be used in preference to terms such as 'legal highs' throughout this thesis.

A further distinction is that of the use of existing medicaments for the purpose of bringing about a psychoactive experience, such as the smoking of hyoscine butylbromide, (Jalali et al., 2014) or the insufflation of gabapentin (Evoy et al., 2018). Medicaments were excluded as psychoactive substances from the Psychoactive Substances Act 2016, those substances listed as controlled, such as morphine are dealt with as part of the Misuse of Drugs Regulations 2001. The MDR 2001 allows for the legal use of substances which would otherwise be illegal if there was not a medical benefit for their use. The use of medicaments in a novel way shall therefore not be considered as a novel psychoactive substance during this research.

This research project incorporates both experimental and literature-based findings. Utilising systematic review to assess the trends arising from NPS in the periods 2011 – 2015, then from 2016 after the introduction of the Psychoactive Substances Act to the present to assess trends since the introduction of the Act. In the experimental arm, Raman spectroscopy will be used to analyse the contents of samples taken from the amnesty bin at Glastonbury Festival 2011. These samples were discarded voluntarily by the attending members of the festival. They were of varying form, shape and colour. A full description of all samples was taken during scanning, however access to this document was restricted whilst the research project was ongoing. Therefore, a full breakdown cannot be provided regarding the nature of the substances.

Use of Raman Spectroscopy will be two-fold, firstly, to investigate whether handheld Raman spectroscopy can be used in rapid-scanning of NPS. Secondly, it will be utilised to see how prevalent NPS were before any major controls were in place from the Government. The overall aim of this research is to critically trends emerging from the use of NPS.

Objectives;

- Investigate the contents of Glastonbury 2011 samples, with the use of handheld spectroscopic techniques.
- Evaluate trends in the years 2011 – 2015, with the use of contemporaneous literature.
- Assess the current prevalence of use and understand policy, using current literature.

During the experimental arm of this research the Bruker BRAVO Duo, handheld Raman analyser was utilised. The basis of which Raman spectroscopy utilises the, 'Raman effect' of the inelastic scattering of light; by using a monochromatic beam of light in the IR region of the electromagnetic spectrum. When the light interacts with a molecule, if it can bring about, 'a change in polarisability' in the molecule, it will be Raman active. Raman spectroscopy is quick and efficient at yielding spectra.

In practice this 'change in polarisability' is the stretching of the bonds within the molecule. As seen in figure 1, two ways in which a bond can stretch is symmetrical and asymmetrical.

Figure 1 - diagram showing the principle of Raman activity, with bonds stretching symmetrically and asymmetrically respectively.

As the bond stretches symmetrically bringing both hydrogen atoms closer or rebounding away, this will induce a dipole moment where the nitrogen will become slightly positive or negative, and hence changes its polarisability. In infrared spectroscopy, this change in polarisability is not necessary and IR spectroscopy can detect asymmetrical bond stretches amongst others.

It does, however, have its drawbacks, this being it is a surface level technique, so if there are multiple Raman active chemicals in a sample, then there will be possible masking. A further in-depth discussion of Raman spectroscopy can be found in chapter 3.1. Raman spectroscopy will be used in this research because of its versatility and quick results. When compared to other techniques, such as chromatography which can take anywhere between 5-90 minutes, Raman is ideal for quickly yielding results. Further, Raman can analyse samples through certain substrates, such as some plastic bags, quartz and glass. This is ideal as the samples will remain in their storage containers and do not need any sample preparation to be analysed. The technique is also non-destructive, so the sample can be retained for future analysis.

Whilst most of these advantages exist within the field of Spectroscopy, Raman was chosen for a couple of reasons. The first being the little-to-none interaction with quartz or silica-based glass. For example, infrared-red spectroscopy will have to some degree an interaction. This is somewhat negated in near-IR, however another advantage Raman has is the fact it will yield only a spectrum for the most prolific Raman active substance in a mixture. When analysing drug mixtures this is hoped to be advantageous. Most drugs are cut with bulking agents, with Raman it is hoped that only the active drug will be seen in the spectrum. With IR, there can be overlapping with mixtures which could obscure identification.

Statistical Analysis

Statistical analysis was used during this research to identify correlations in the data gained from the scanning of Glastonbury samples, the scheme of which can be found in chapter 2.1. After the Raman analyser had been used, but before the spectra could be analysed, the data needed to be sorted so that alike compounds are grouped together for identification. Statistical analysis is the most efficient and effective way of doing this grouping.

The statistical analytical tools used were principle component analysis (PCA), k-means clustering and hierarchal clustering.

Data Collection

The substances for analysis were self-surrendered by attending members of the Glastonbury festival 2011. Amnesty bins were placed by Avon and Somerset Constabulary for attendees to discard of any illicit materials without any legal repercussions. Each of the samples were collected on each day of the festival from Thursday 23rd through to Sunday 26th June 2011.

Before this research the original samples wrappings were discarded when transferred into glass vials. This work was undertaken by Bournemouth Students on the MSc Toxicology, by research under the supervision of Professor M. D. Osselton, when transferred the samples were assigned a batch letter and number. The batch letter corresponds to the day on which the substance was placed into the amnesty bin; Thursday was batch A and each day subsequent being, batch B, C and D.

In total there were 260 samples across all four batches, however not all were Raman active. Three scans were taken of each sample, totalling 607 scans. In total 126 samples were Raman active and scans were able to be taken giving 378 scans able for analysis.

Data Manipulation

The three scans for each sample were loaded into Spectragryph v1.2.1, the mean-average was taken of each, to yield one spectrum to be smoothed. Standard normal variates (SNV) was used to smooth the averaged spectrum, which was then derivatised. First-order derivative was used, which is the rate of change of intensity against wavelength (Owen, 1995).

For the statistical manipulation, RStudio version 3.6 was used. The PCA models, scree plots, k-means plots and dendrograms were all produced with RStudio v3.6.

Principles

Principle component analysis (PCA) is a statistical analysis tool used for multivariate analysis, it compares variables from a group of samples, e.g. population groupings and blood types, table 1. This is based upon the variance, which is defined as data-distance from the mean. Thus, alike data will group together having similar variances.

Table 1- Example of blood types within population groups.

	Population 1	Population 2	Population 3	Population 4	Population 5
Type A	10	7	9	2	2
Type B	8	9	6	1	3

These samples could then be plotted in order of value and a correlation will start to be seen, see Figure 2. As can be seen in the example, population 1, 2 and 3 group together, with 4 and 5 grouping together.

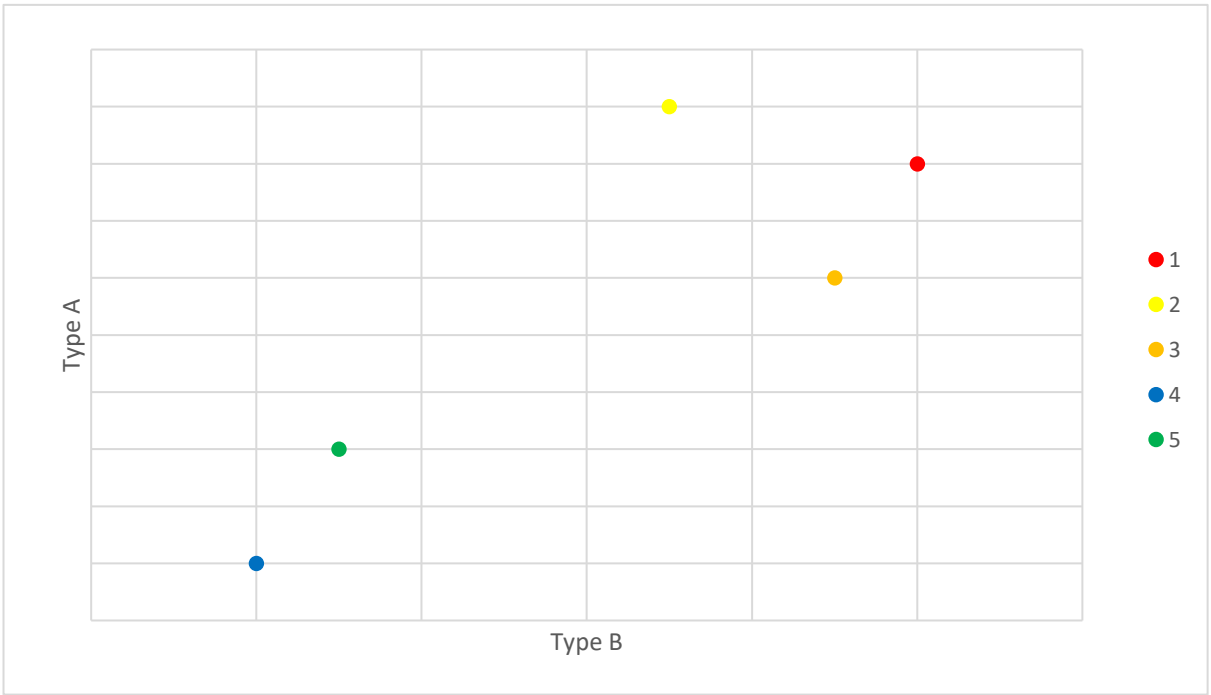


Figure 2 – Graphical Representation of Table 1, showing an example of blood types amongst population. The key corresponds to the population groups in Table 1.

The centre of the dataset is then calculated by taking the median average, then the dataset is shifted so the average of the data becomes the origin (Miller and Miller, 1988). It should be noted this shift in the data does not change the relative positions of the data; Figure 3 shows this shift. Once this data has been shifted a trend line can then be put in that goes through the origin. To decide whether the line is of best fit, the line should minimise the distance from the data points to the line.

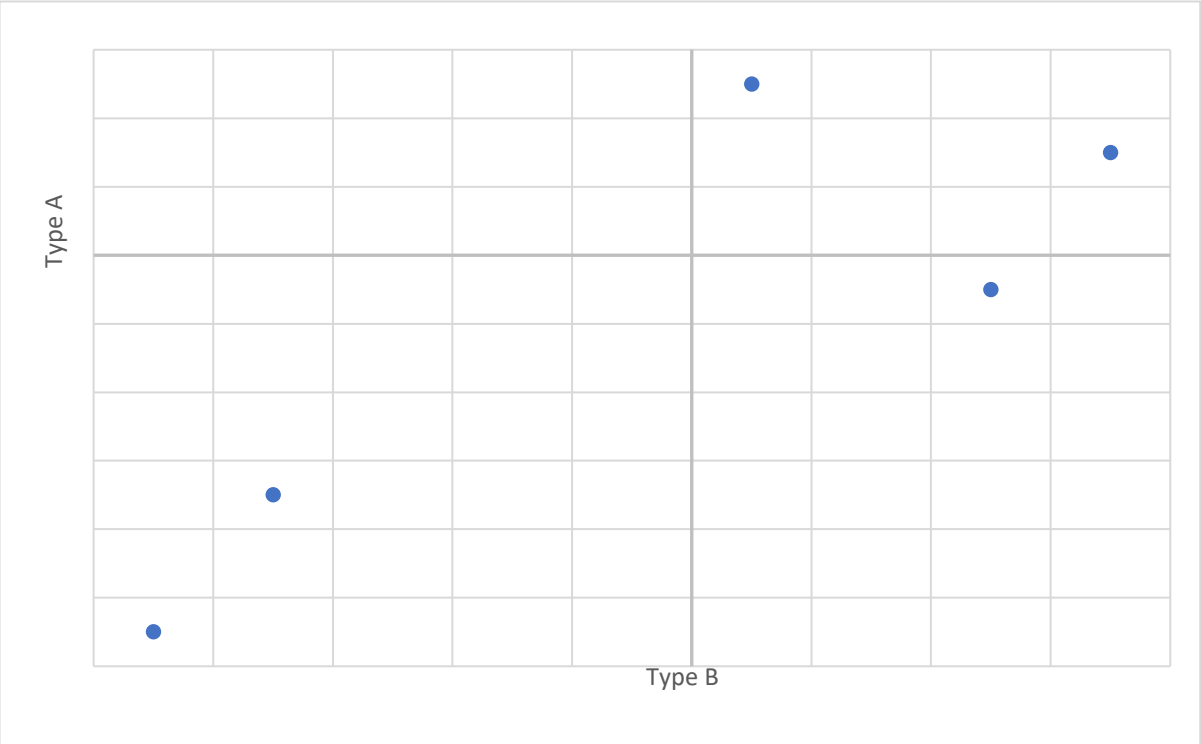


Figure 3 – graph displaying the same data points as Figure 2, with the data having been 'centre-shifted.' Centre-shift is to place the mean of the data group upon the origin (0,0).

As can be seen in Figure 4, the trend line in (a) has minimised the distance from the data points whilst remaining the best fit, unlike (b) which has greater distance from the data points therefore not being of best fit. This trendline is called Principle Component 1 (PC1), from it is taken the gradient, which in this example is 0.75. Using trigonometry, what is termed singular vector can be calculated, this is as if a triangle were in place, with PC1 being the hypotenuse, the distance of the hypotenuse is the single vector (Miller and Miller, 1988).

For the PC1, the opposite and adjacent sides of the triangle calculation will become known as the loading scores. In this example, the loading scores would be 0.9 and 0.0998, this is the ratio for PC1 that type A and type B is found for this dataset (Graham, 1993).

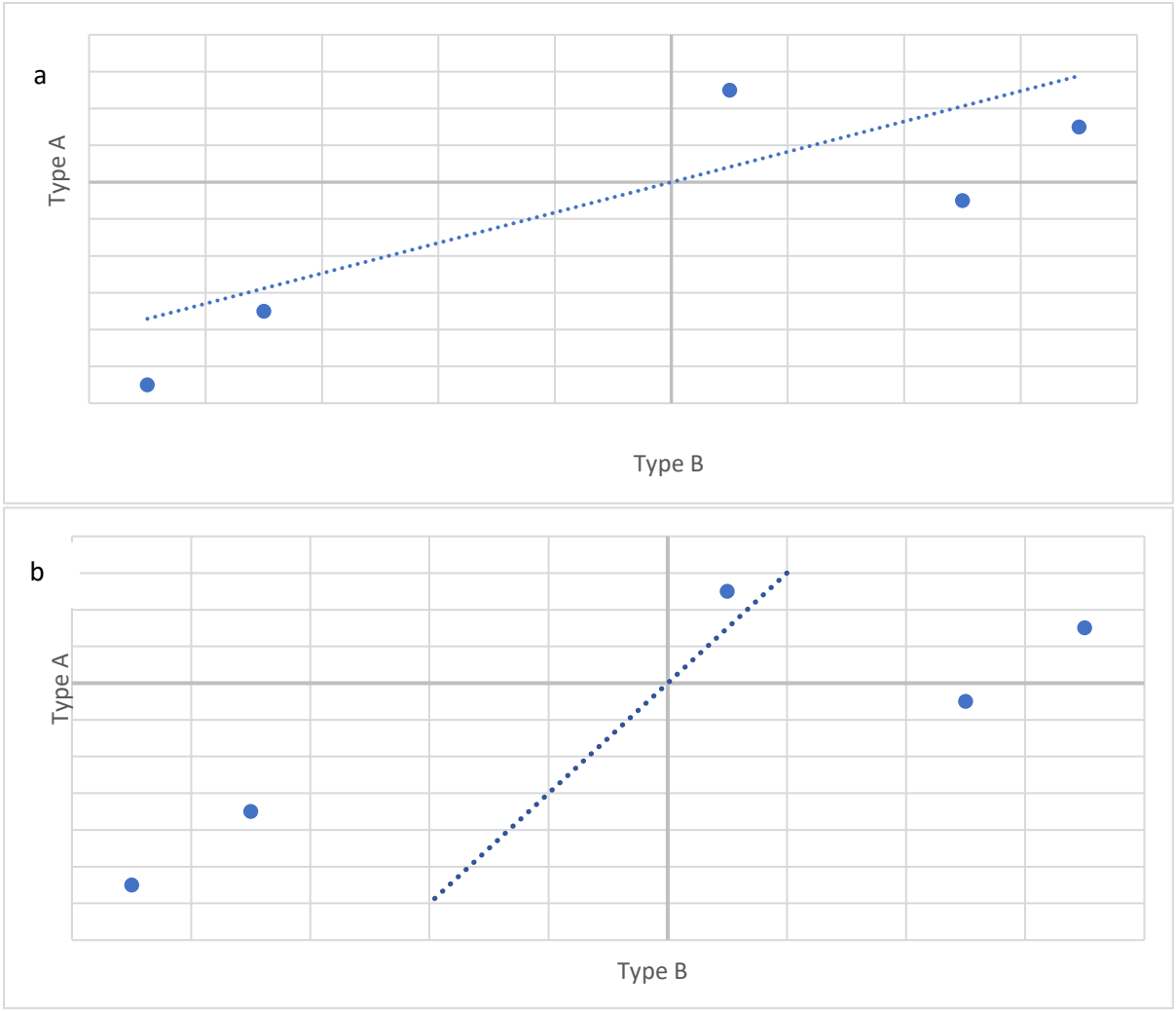


Figure 4 – Diagram showing the optimal placement of a trendline using the example dataset, blood types amongst population. (a) shows optimal placement as it crosses the origin, minimises the distance from the datapoint whilst remaining of best fit. (b) shows how a trendline of non-optimal placement as it does not minimise the distance from all datapoints, whilst remaining of best fit.

To calculate PC2 for a 2-D system, this is simply adding a line at a right angle to PC1, also going through the origin (Miller and Miller, 1988). Once PC1 and PC2 are in place, the original axis can be removed, and the PC axes are then rotated so they become the x and y axis. Figure 5 shows the PCs after the axes have been removed, before being rotated.

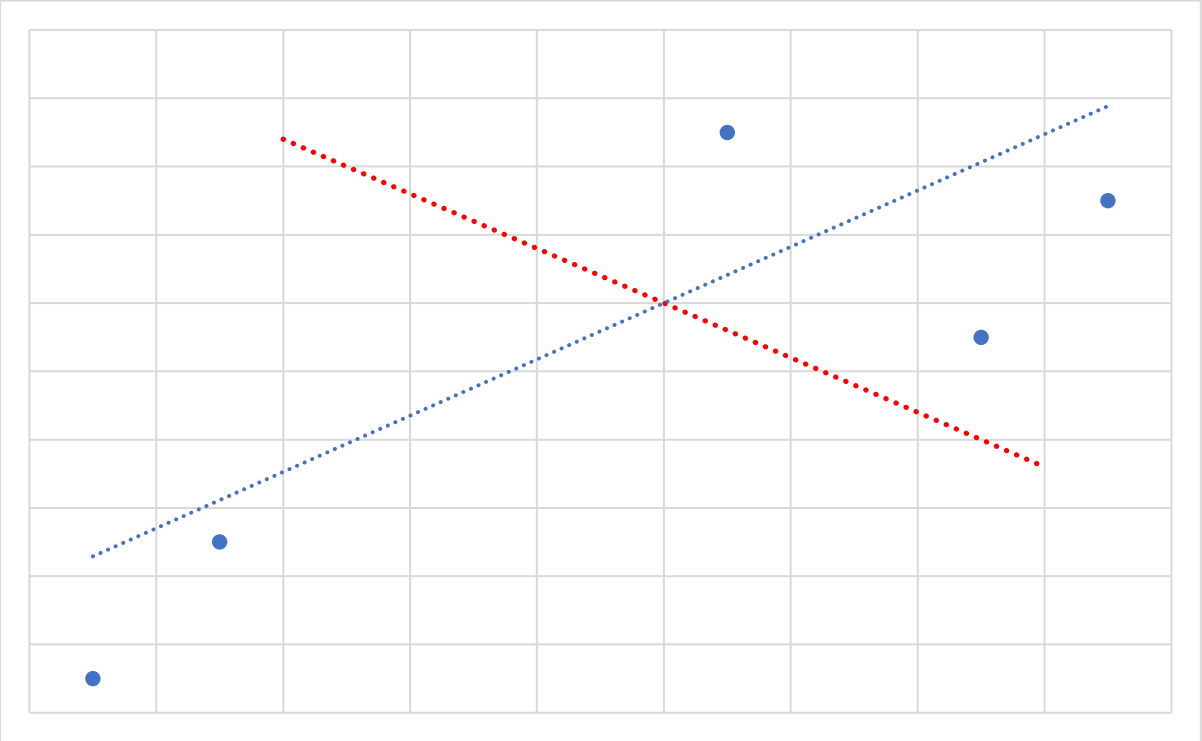


Figure 5 – a diagram showing the placement of principles components in red (PC1) and blue (PC2) using the example dataset, blood types amongst populations.

The loading score is then squared before being divided by the total variance. For this example, the 0.9 and 0.0998 would become 99.9% and 0.998%, meaning that blood type A accounts for 99.9% of the variance in the population groups and blood type B accounts for 0.998% of variance in the population groups. The variance will then be plotted onto a scree plot, Figure 6 shows a scree plot for the example. Figure 7 shows the complete PCA model.

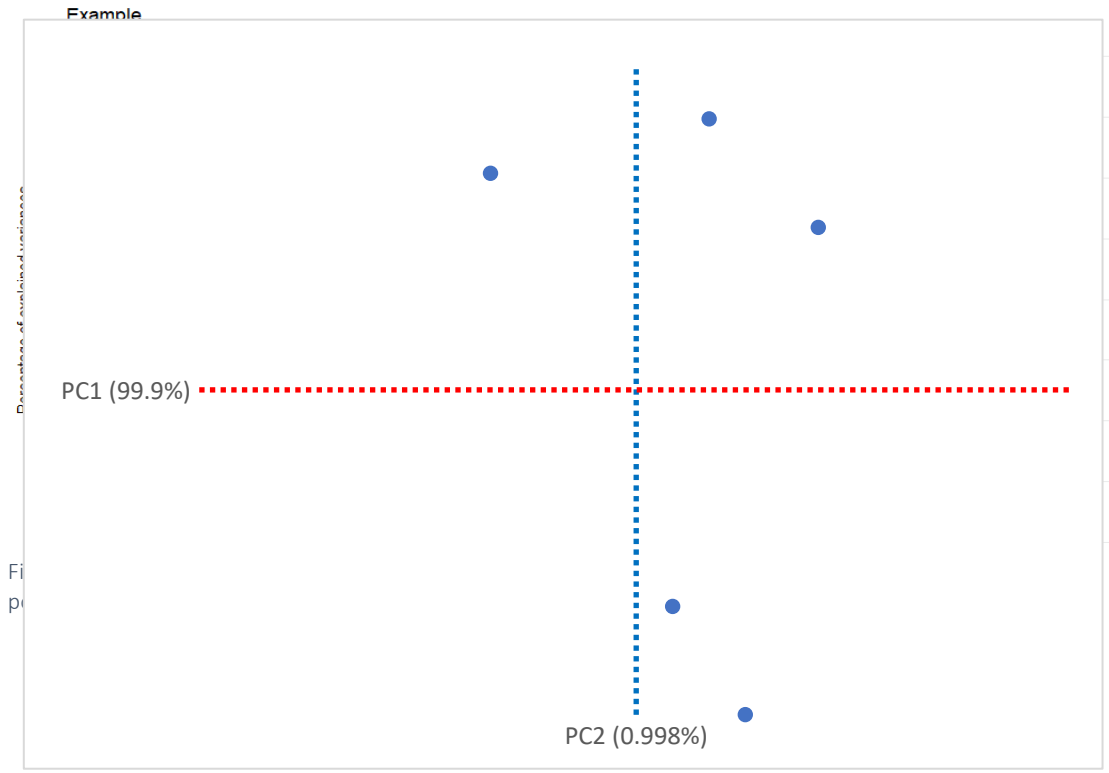


Figure 7 – The completed PCA model for the example dataset blood types amongst populations.

Principle component analysis can be used to find correlations in datasets. Using the example PCA, the grouping in the right upper quadrant may suggest that in the two separate population samples, there may be a link, such as being the in the same ethnic group. This principle has been used during the experimental arm of this research with cluster analysis.

Cluster analysis can be done with the use of statistics; k-means analysis analyses the distance a datapoint is to the cluster mean; the datapoint then gets grouped to the closest cluster mean (MacQueen, 1967). K-means analysis may not always choose the best fit, so many iterations can be processed to assess how many clusters are statistically ideal.

The Hartigan-Wong (1979) algorithm is used during this research; this assigns a random number for the start of the iterations, meaning a wide variety clusters can be analysed. These iterations can be plotted to a line graph, as seen in Figure 8.

From the plot the ideal number of clusters is seen as the point before there is a plateau. In the example plot, this would be 3 clusters. Once the ideal number of clusters has been calculated it then needs to be visualised so the datapoints can be grouped for further analysis.

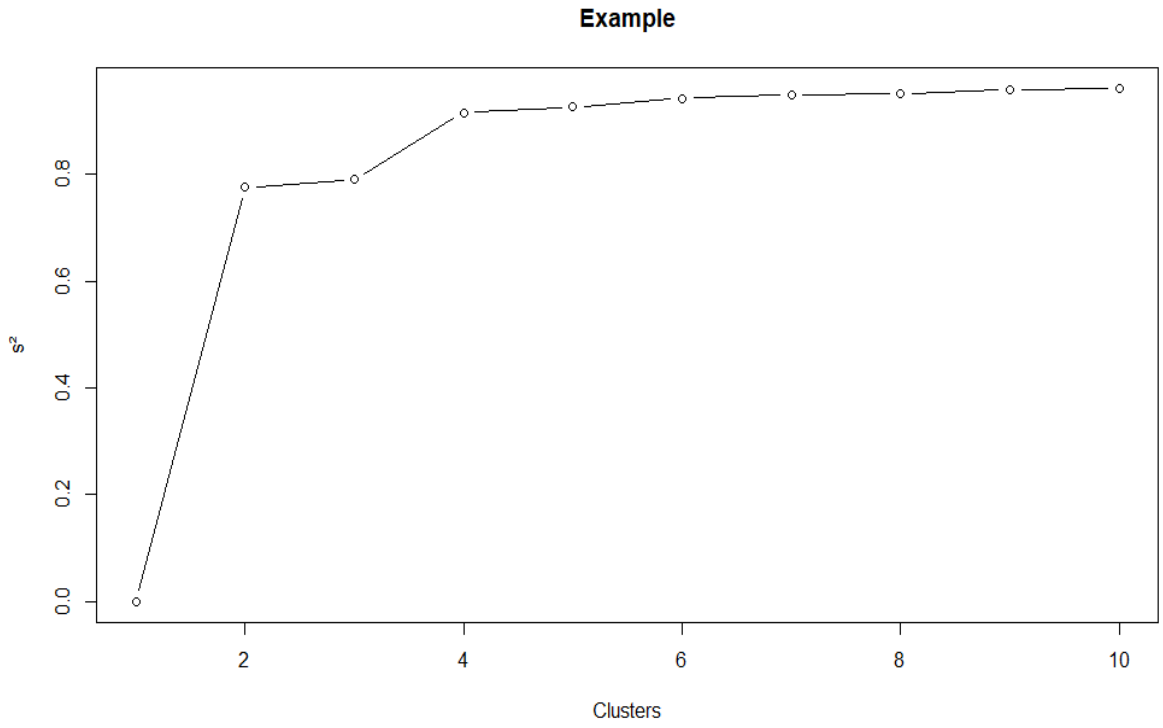


Figure 8 – A k-means plot for the example dataset, blood types amongst populations.

Dendrograms are the visualisation of hierarchical clustering. Like k-means clustering, hierarchal clustering is based on distance. The mid-point distances between to datapoint joins the two datapoints and become a single representation of two datapoints, this is known agglomeration, shown in Figure 9.

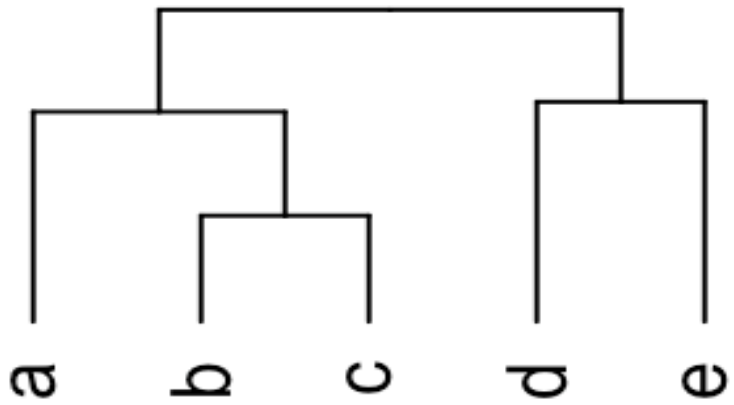
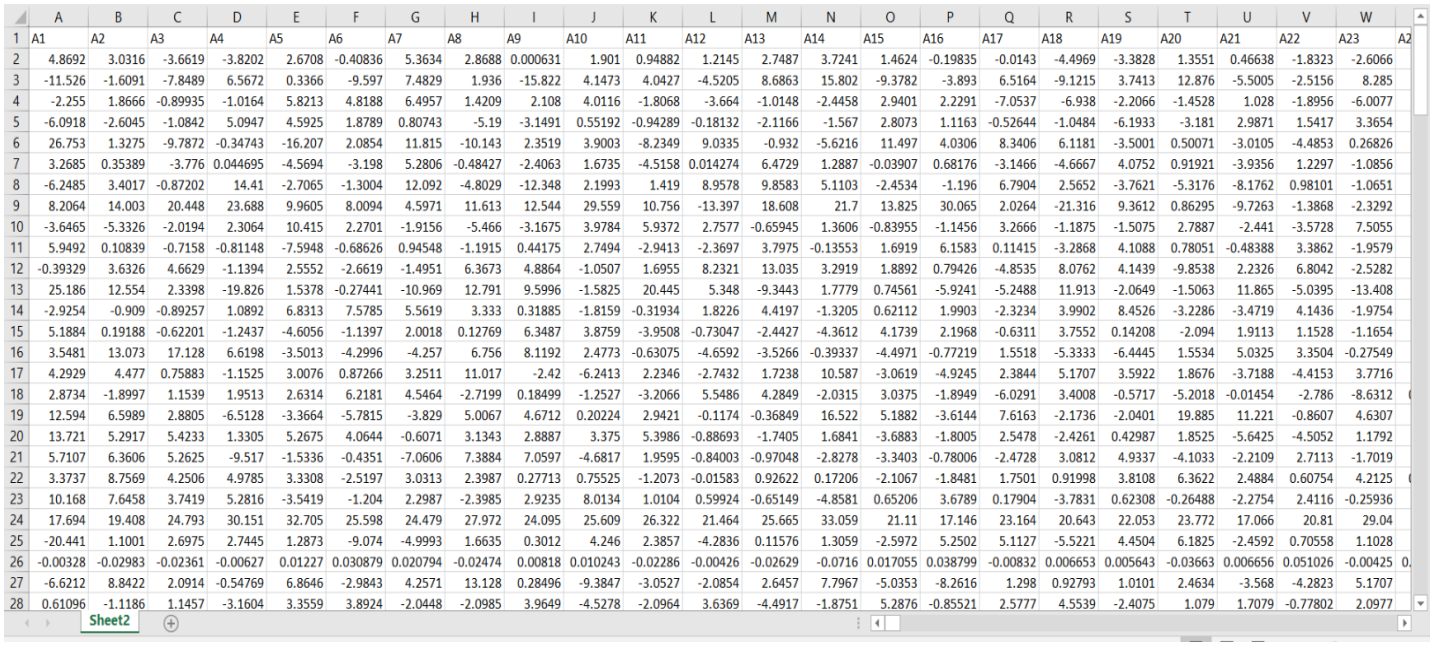


Figure 9 – A diagram showing the process of agglomeration in a dendrogram.

As with k-means clustering, the datapoints that are close in distance will more than likely be alike in nature, so the single datapoint will cluster alike datapoints. A dendrogram is the visualisation of this clustering. This clustering can be taken one step further with the use of k-means clustering. Once the ideal number of clusters has been decided with k-means, this can then separate groups of data on the dendrogram into clusters that are alike.

Experimental

PCA was used to analyse each batch of substances individually. The aim was to identify clusters within the data which would then identify substances similar in class to be analysed for the contents. To facilitate this, each derivatised spectrum of each batch was loaded into an excel sheet, with the samples running sequentially across the columns. When the spectrum is produced by the Raman analyser, the sampling points along the wavelength will be the same across all spectra. These numbers are not included in the PCA as it is not needed to carry out the PCA. Figure 10 shows the excel sheet.



	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W
1	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10	A11	A12	A13	A14	A15	A16	A17	A18	A19	A20	A21	A22	A23
2	4.8692	3.0316	-3.6619	-3.8202	2.6708	-0.40836	5.3634	2.8688	0.000631	1.901	0.94882	1.2145	2.7487	3.7241	1.4624	-0.19835	-0.0143	-4.4969	-3.3828	1.3551	0.46638	-1.8323	-2.6066
3	-11.526	-1.6091	-7.8489	6.5672	0.3366	-9.597	7.4829	1.936	-15.822	4.1473	4.0427	-4.5205	8.6863	15.802	-9.3782	-3.893	6.5164	-9.1215	3.7413	12.876	-5.5005	-2.5156	8.285
4	-2.255	1.8666	-0.89935	-1.0164	5.8213	4.8188	6.4957	1.4209	2.108	4.0116	-1.8068	-3.664	-1.0148	-2.4458	2.9401	2.2291	-7.0537	-6.938	-2.2066	-1.4528	1.028	-1.8956	-6.0077
5	-6.0918	-2.6045	-1.0842	5.0947	4.5925	1.8789	0.80743	-5.19	-3.1491	0.55192	-0.94289	-0.18132	-2.1166	-1.567	2.8073	1.1163	-0.52644	-1.0484	-6.1933	-3.181	2.9871	1.5417	3.3654
6	26.753	1.3275	-9.7872	-0.34743	-16.207	2.0854	11.815	-10.143	2.3519	3.9003	-8.2349	9.0335	-0.932	-5.6216	11.497	4.0306	8.3406	6.1181	-3.5001	0.50071	-3.0105	-4.4853	0.26826
7	3.2685	0.35389	-3.776	0.044695	-4.5694	-3.198	5.2806	-0.48427	-2.4063	1.6735	-4.5158	0.014274	6.4729	1.2887	-0.03907	0.68176	-3.1466	-4.6667	4.0752	0.91921	-3.9356	1.2297	-1.0856
8	-6.2485	3.4017	-0.87202	14.41	-2.7065	-1.3004	12.092	-4.8029	-12.348	2.1993	1.419	8.9578	9.8583	5.1103	-2.4534	-1.196	6.7904	2.5652	-3.7621	-5.3176	-8.1762	0.98101	-1.0651
9	8.2064	14.003	20.448	23.688	9.9605	8.0094	4.5971	11.613	12.544	29.559	10.756	-13.397	18.608	21.7	13.825	30.065	2.0264	-21.316	9.3612	0.86295	-9.7263	-1.3868	-2.3292
10	-3.6465	-5.3326	-2.0194	2.3064	10.415	2.2701	-1.9156	-5.466	-3.1675	3.9784	5.9372	2.7577	-0.65945	1.3606	-0.83955	-1.1456	3.2666	-1.1875	-1.5075	2.7887	-2.441	-3.5728	7.5055
11	5.9492	0.10839	-0.7158	-0.81148	-7.5948	-0.68626	0.94548	-1.1915	0.44175	2.7494	-2.9413	-2.3697	3.7975	-0.13553	1.6919	6.1583	0.11415	-3.2868	4.1088	0.78051	-0.48388	3.3862	-1.9579
12	-0.39329	3.6326	4.6629	-1.1394	2.5552	-2.6619	-1.4951	6.3673	4.8864	-1.0507	1.6955	8.2321	13.035	3.2919	1.8892	0.79426	-4.8535	8.0762	4.1439	-9.8538	2.2326	6.8042	-2.5282
13	25.186	12.554	2.3398	-19.826	1.5378	-0.27441	-10.969	12.791	9.5996	-1.5825	20.445	5.348	-9.3443	1.7779	0.74561	-5.9241	-5.2488	11.913	-2.0649	-1.5063	11.865	-5.0395	-13.408
14	-2.9254	-0.909	-0.89257	1.0892	6.8313	7.5785	5.5619	3.333	0.31885	-1.8159	-0.31934	1.8226	4.4197	-1.3205	0.62112	1.9903	-2.3234	3.9902	8.4526	-3.2286	-3.4719	4.1436	-1.9754
15	5.1884	0.19188	-0.62201	-1.2437	-4.6056	-1.1397	2.0018	0.12769	6.3487	3.8759	-3.9508	-0.73047	-2.4427	-4.3612	4.1739	2.1968	-0.6311	3.7552	0.14208	-2.094	1.9113	1.1528	-1.1654
16	3.5481	13.073	17.128	6.6198	-3.5013	-4.2996	-4.257	6.756	8.1192	2.4773	-0.63075	-4.6592	-3.5266	-0.39337	-4.4971	-0.77219	1.5518	-5.3333	-6.4445	1.5534	5.0325	3.3504	-0.27549
17	4.2929	4.477	0.75883	-1.1525	3.0076	0.87266	3.2511	11.017	-2.42	-6.2413	2.2346	-2.7432	1.7238	10.587	-3.0619	-4.9245	2.3844	5.1707	3.5922	1.8676	-3.7188	-4.4153	3.7716
18	2.8734	-1.8997	1.1539	1.9513	2.6314	6.2181	4.5464	-2.7199	0.18499	-1.2527	-3.2066	5.5486	4.2849	-2.0315	3.0375	-1.8949	-6.0291	3.4008	-0.5717	-5.2018	-0.01454	-2.786	-8.6312
19	12.594	6.5989	2.8805	-6.5128	-3.3664	-5.7815	-3.829	5.0067	4.6712	0.20224	2.9421	-0.1174	-0.36849	16.522	5.1882	-3.6144	7.6163	-2.1736	-2.0401	19.885	11.221	-0.8607	4.6307
20	13.721	5.2917	5.4233	1.3305	5.2675	4.0644	-0.6071	3.1343	2.8887	3.375	5.3986	-0.88693	-1.7405	1.6841	-3.6883	-1.8005	2.5478	-2.4261	0.42987	1.8525	-5.6425	-4.5052	1.1792
21	5.7107	6.3606	5.2625	-9.517	-1.5336	-0.4351	-7.0606	7.3884	7.0597	-4.6817	1.9595	-0.84003	-0.97048	-2.8278	-3.3403	-0.78006	-2.4728	3.0812	4.9337	-4.1033	-2.2109	2.7113	-1.7019
22	3.3737	8.7569	4.2506	4.9785	3.3308	-2.5197	3.0313	2.3987	0.27713	0.75525	-1.2073	-0.01583	0.92622	0.17206	-2.1067	-1.8481	1.7501	0.91998	3.8108	6.3622	2.4884	0.60754	4.2125
23	10.168	7.6458	3.7419	5.2816	-3.5419	-1.204	2.2987	-2.3985	2.9235	8.0134	1.0104	0.59924	-0.65149	-4.8581	0.65206	3.6789	0.17904	-3.7831	0.62308	-0.26488	-2.2754	2.4116	-0.25936
24	17.694	19.408	24.793	30.151	32.705	25.598	24.479	27.972	24.095	25.609	26.322	21.464	25.665	33.059	21.11	17.146	23.164	20.643	22.053	23.772	17.066	20.81	29.04
25	-20.441	1.1001	2.6975	2.7445	1.2873	-9.074	-4.9993	1.6635	0.3012	4.246	2.3857	-4.2836	0.11576	1.3059	-2.5972	5.2502	5.1127	-5.5221	4.4504	6.1825	-2.4592	0.70558	1.1028
26	-0.00328	-0.02983	-0.02361	-0.00627	0.01227	0.030879	0.020794	-0.02474	0.00818	0.010243	-0.02286	-0.00426	-0.02629	-0.0716	0.017055	0.038799	-0.00832	0.006653	0.005643	-0.03663	0.006656	0.051026	-0.00425
27	-6.6212	8.8422	2.0914	-0.54769	6.8646	-2.9843	4.2571	13.128	0.28496	-9.3847	-3.0527	-2.0854	2.6457	7.7967	-5.0353	-8.2616	1.298	0.92793	1.0101	2.4634	-3.568	-4.2823	5.1707
28	0.61096	-1.1186	1.1457	-3.1604	3.3559	3.8924	-2.0448	-2.0985	3.9649	-4.5278	-2.0964	3.6369	-4.4917	-1.8751	5.2876	-0.85521	2.5777	4.5539	-2.4075	1.079	1.7079	-0.77802	2.0977

Sheet2

Figure 10 – image of the excel sheet which has all the derivatised spectra in numerical data for batch A, ready for PCA computation in RStudio.

Once the excel sheet had been compiled, it was then imported into RStudio, which computationally produces the PCA model. Once the PCA model has been produced, further statistical analysis can take place in RStudio which further processes the statistical manipulation. Figures 11 – 14, show each of the PCA models of each batch before any further statistical analysis took place; Appendix A shows the scree plots for each batch.

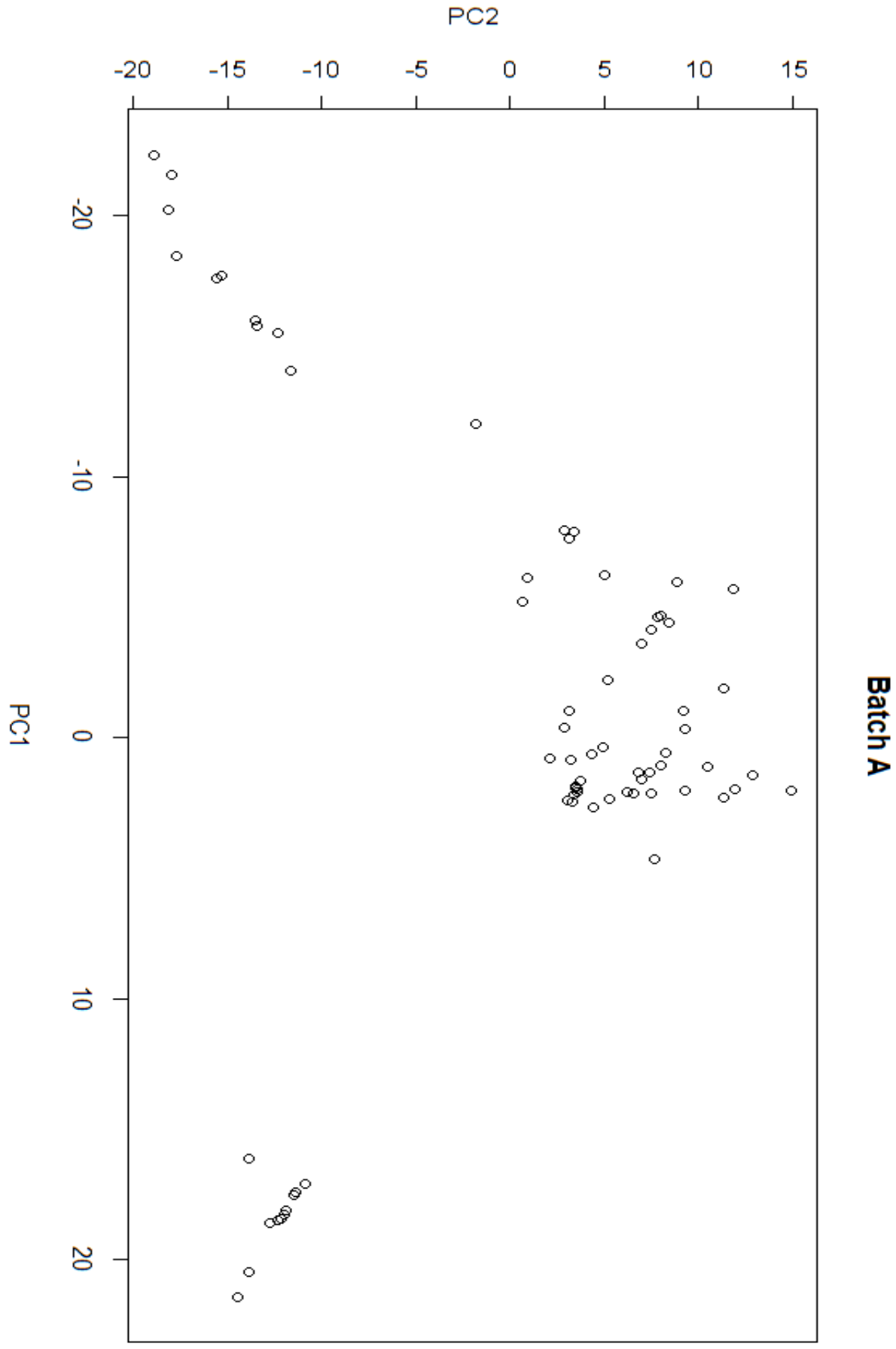


Figure 11 – PCA model for Batch A of the scanned samples taken from the amnesty bins place at the Glastonbury festival 2011, before any further statistical analysis has taken place.

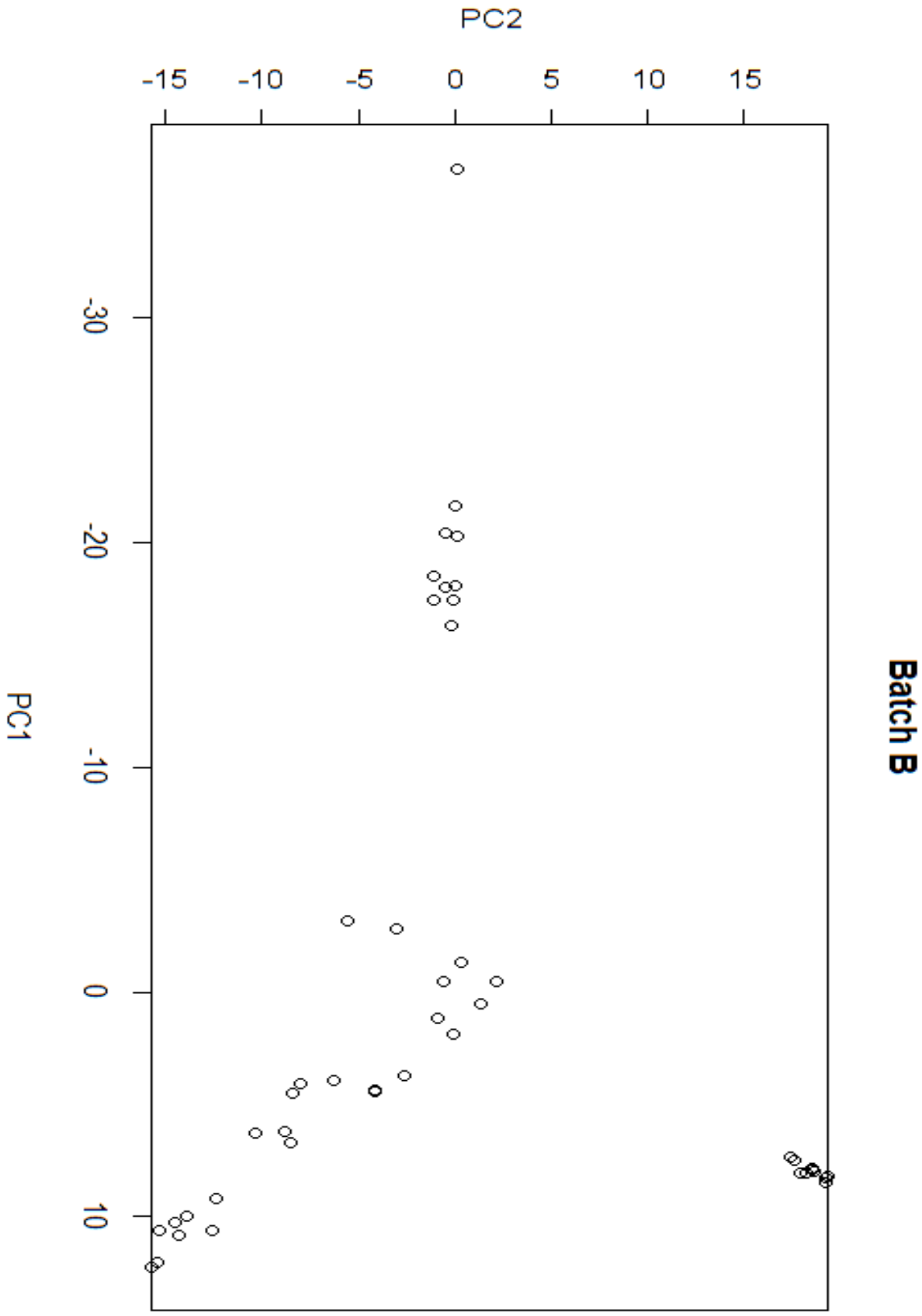


Figure 12 – PCA model for Batch B of the scanned samples taken from the amnesty bins place at the Glastonbury festival 2011, before any further statistical analysis has taken place.

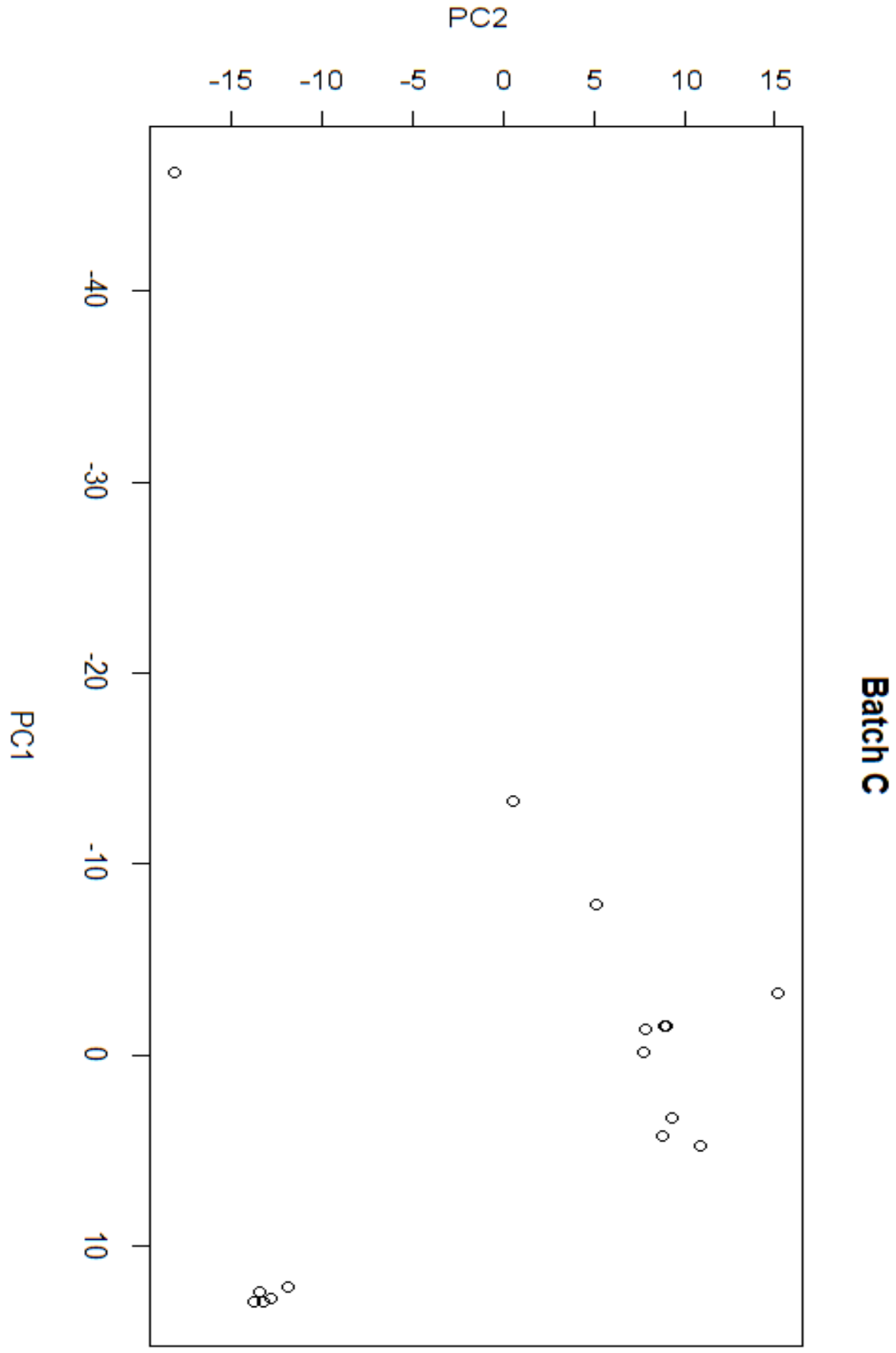


Figure 13 - PCA model for Batch C of the scanned samples taken from the amnesty bins place at the Glastonbury festival 2011, before any further statistical analysis has taken place.

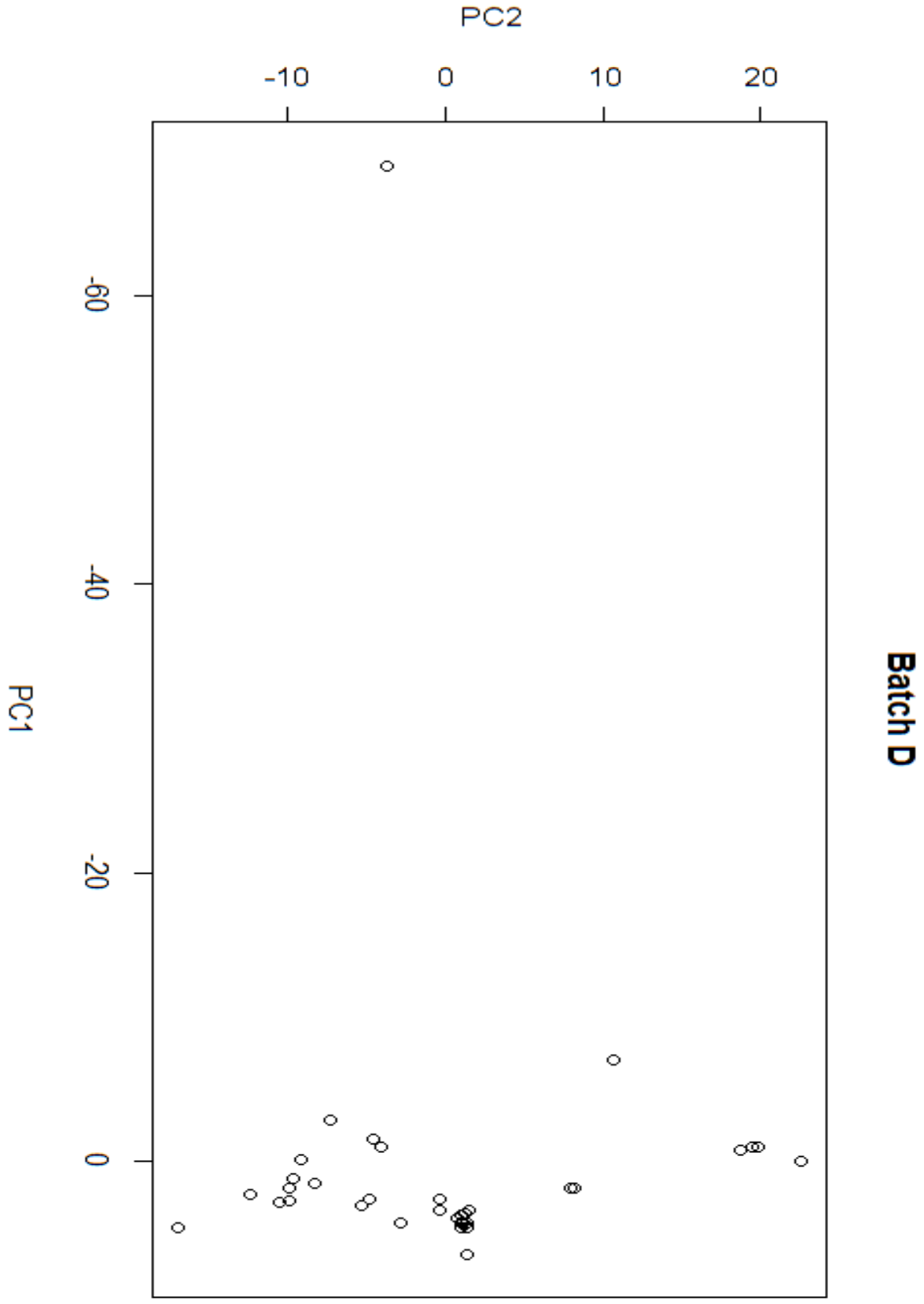


Figure 14 - PCA model for Batch D of the scanned samples taken from the amnesty bins place at the Glastonbury festival 2011, before any further statistical analysis has taken place.

Whilst some clustering can be identified, K-means clustering was utilised to distinguish difficult to see clusters, with Figures 15 - 18 showing the line plots for each set of iterations. From each of the plots: Batch A saw that 5 clusters were ideal; Batch B had 5; Batch C had 3 and batch D had 4.

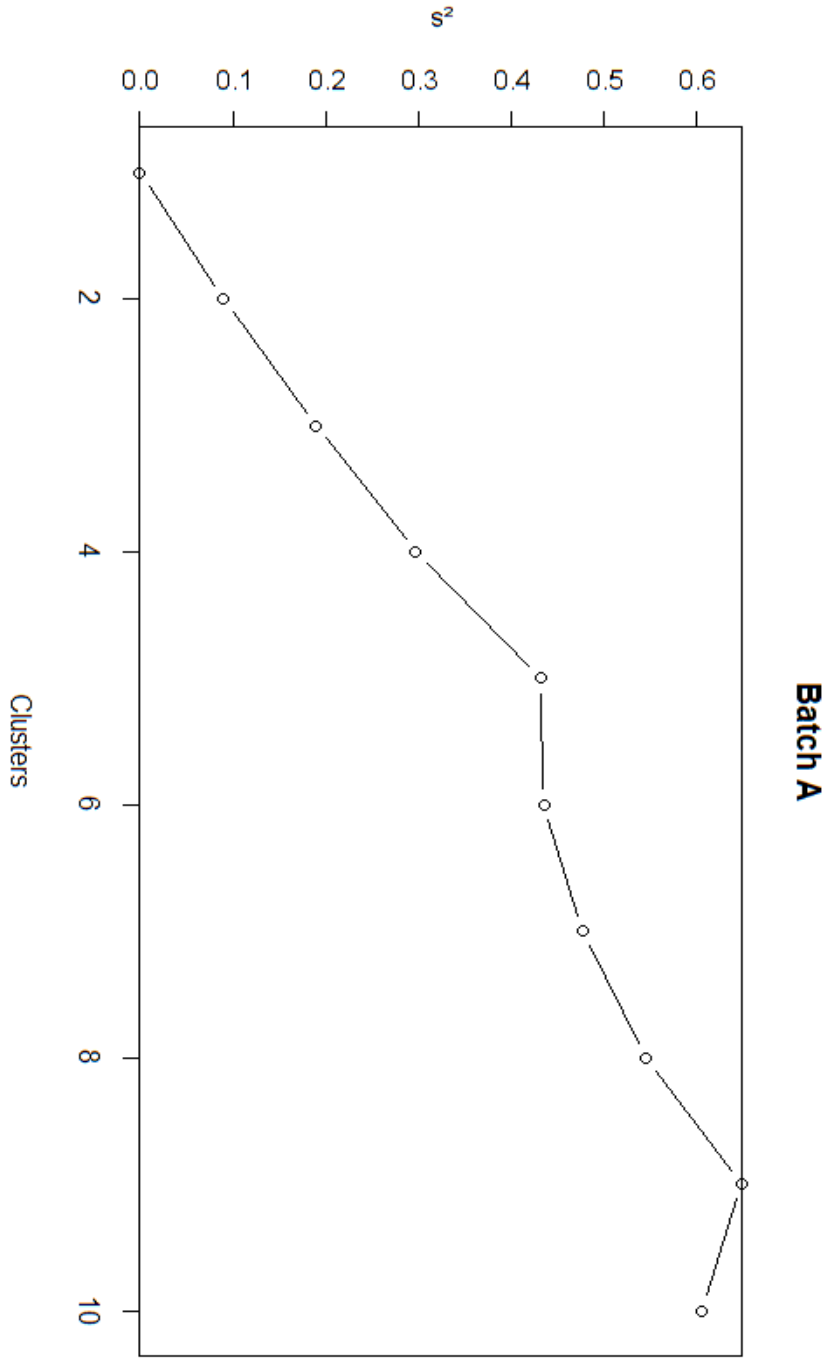


Figure 15 – k-means plot for Batch A of the scanned samples taken from the amnesty bins placed at the Glastonbury Festival 2011.

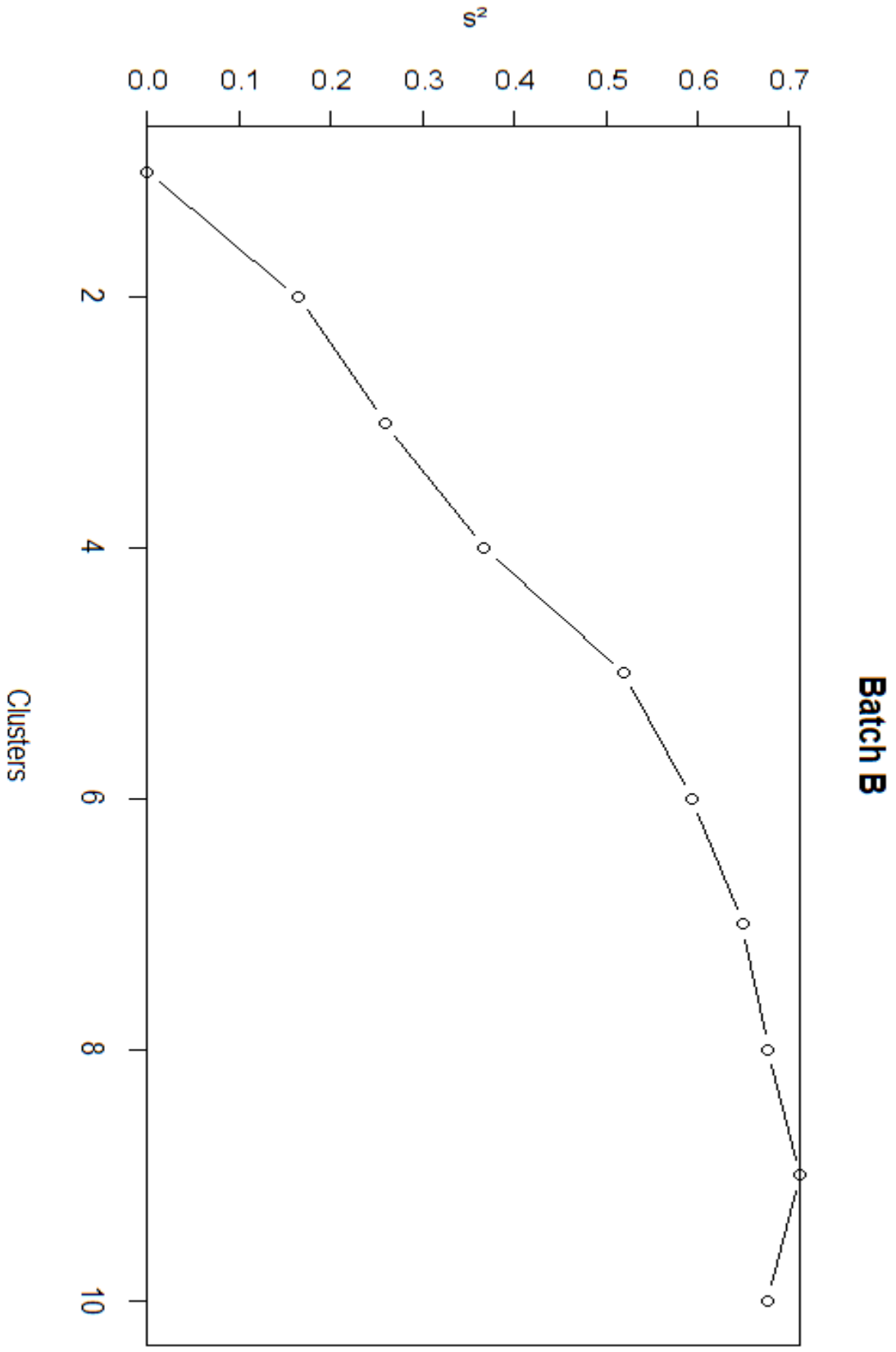


Figure 16 – k-means plot for Batch B of the scanned samples taken from the amnesty bins placed at the Glastonbury Festival 2011.

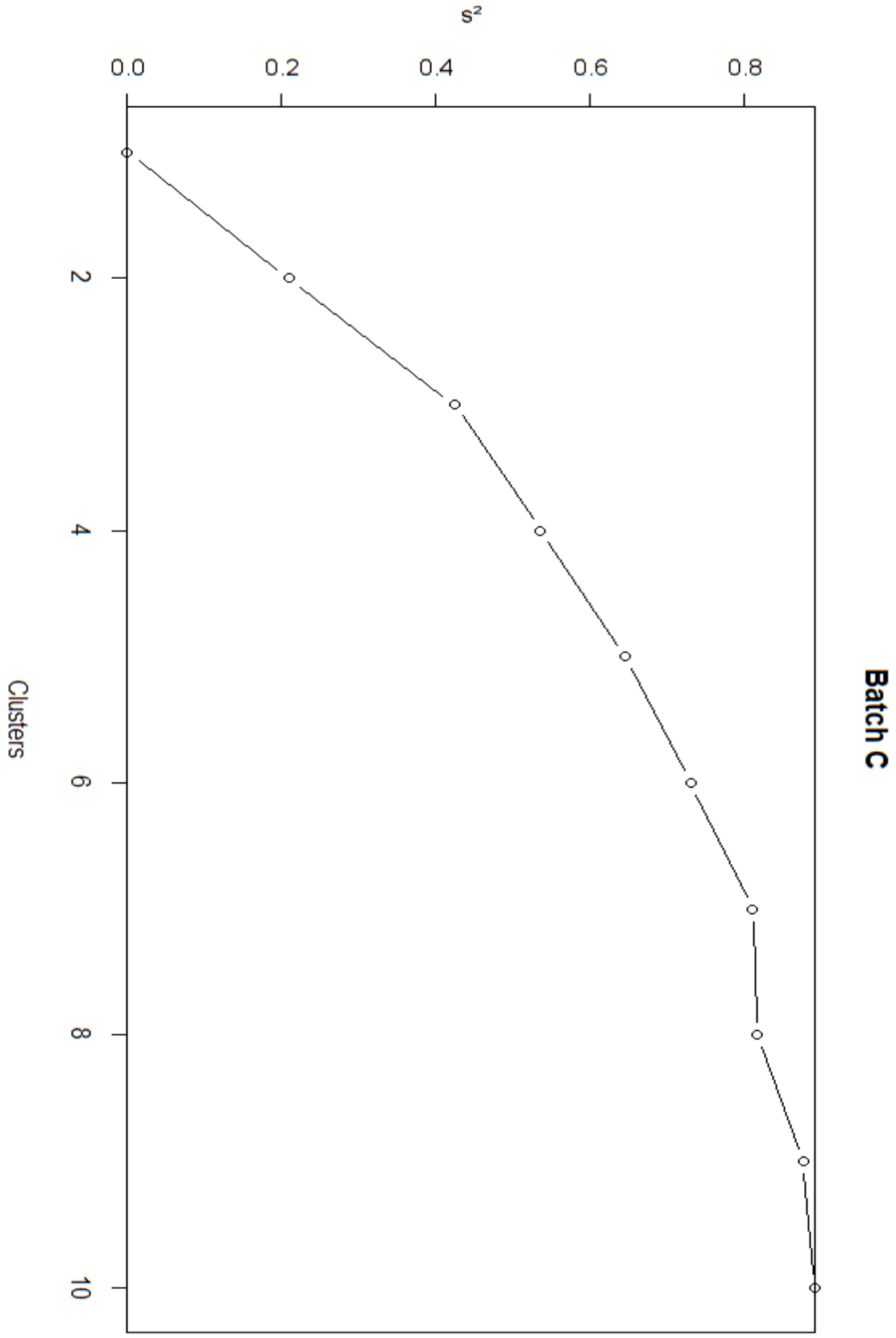


Figure 17 – k-means plot for Batch C of the scanned samples taken from the amnesty bins placed at the Glastonbury Festival 2011.

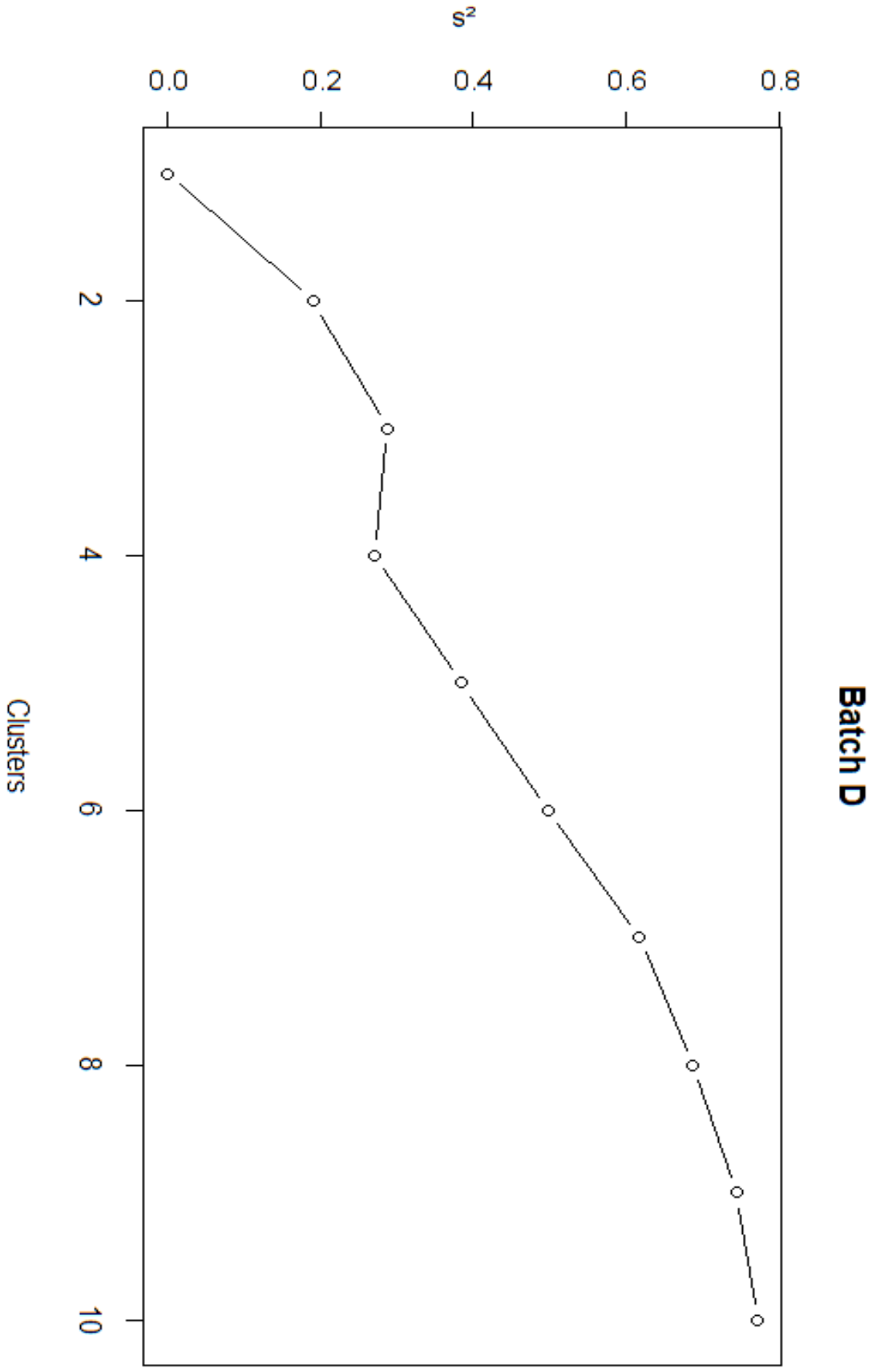


Figure 18 - k-means plot for Batch D of the scanned samples taken from the amnesty bins placed at the Glastonbury Festival 2011.

A dendrogram was made for each of the batches. This showed the substances and how they clustered; Figures 19 – 21 show each batch. These clusters can then be projected onto the individual batch PCA model, which is seen in Figures 22 – 25. The PCA model can then be checked to see if the k-means has the ideal number of clusters and whether the dendrogram has a good split of the data. The datapoint on the PCA in figures 22m-25, have been change to circles for ease of viewability. When checking the dendrogram spacing, the datapoint will correspond with a specific substance, e.g. A1, or B3.

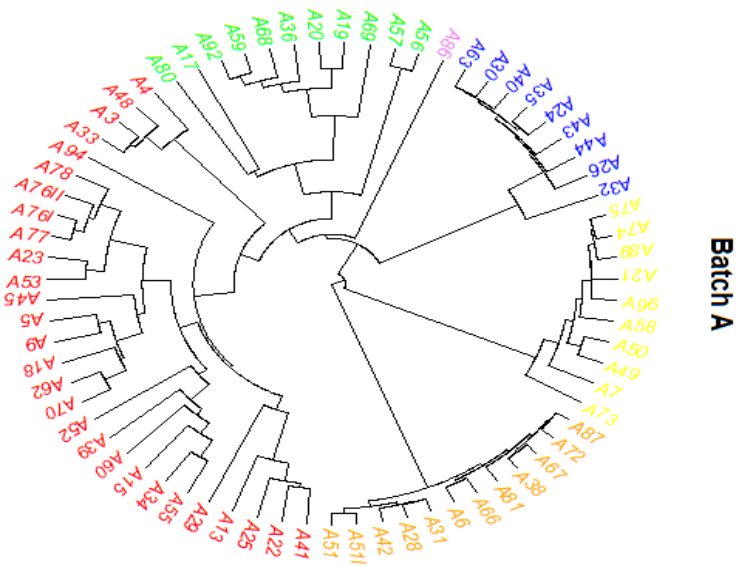


Figure 19 – Dendrogram plot with the ideal number of clusters as obtained from k-means plot (Figure 15), the colours used to aid in differentiation of the clusters. This dendrogram is for batch A of the scanned samples taken from the amnesty bins placed at Glastonbury Festival 2011.

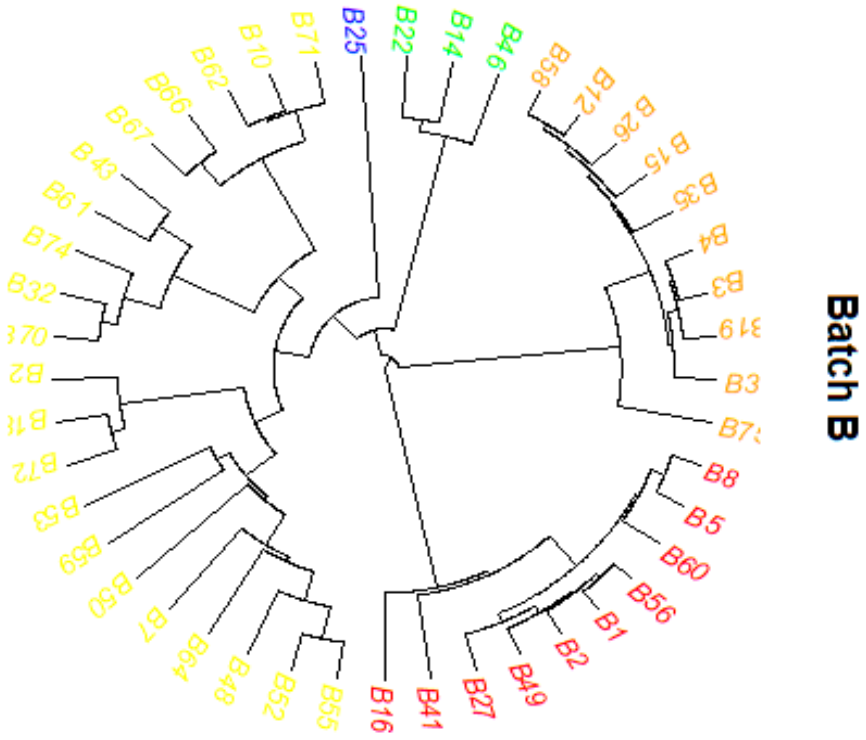


Figure 20 - Dendrogram plot with the ideal number of clusters as obtained from k-means plot (Figure 16), the colours used to aid in differentiation of the clusters. This dendrogram is for batch B of the scanned samples taken from the amnesty bins placed at Glastonbury Festival 2011.

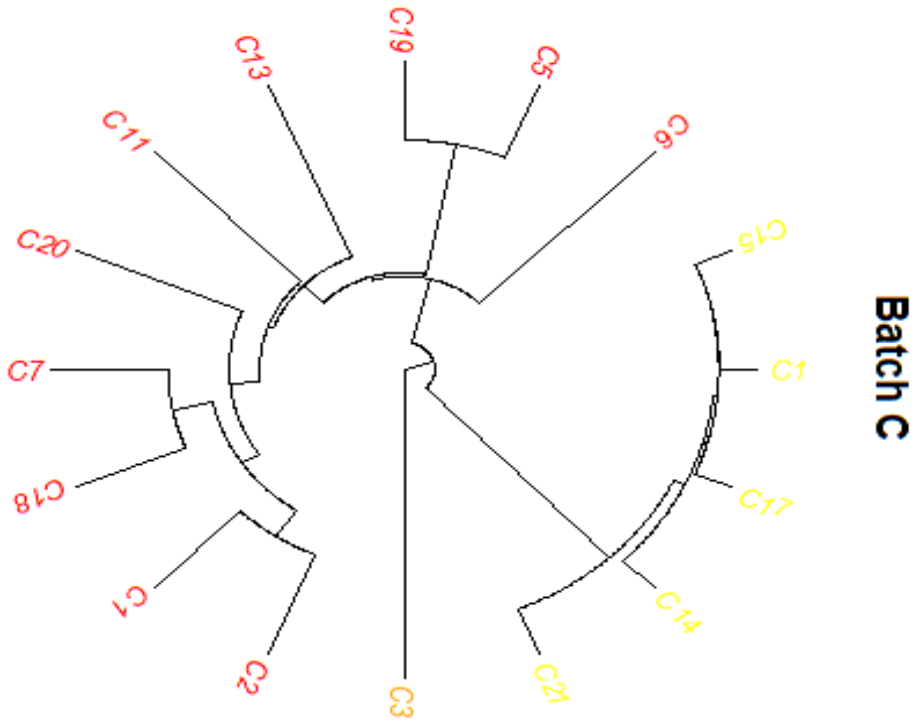


Figure 21 - Dendrogram plot with the ideal number of clusters as obtained from k-means plot (Figure 17), the colours used to aid in differentiation of the clusters. This dendrogram is for batch C of the scanned samples taken from the amnesty bins placed at Glastonbury Festival 2011.

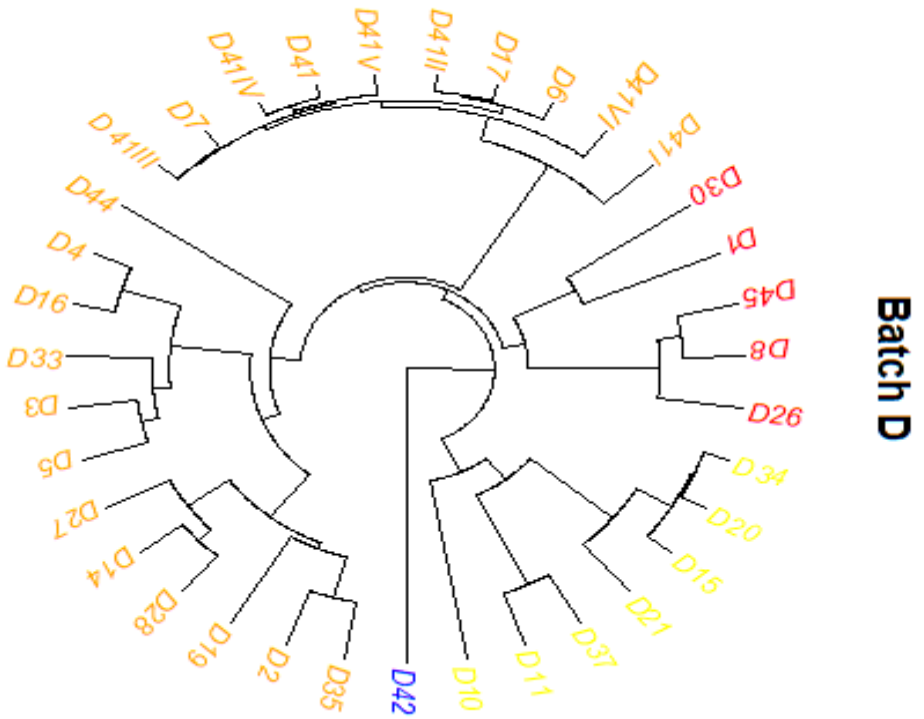


Figure 22 - Dendrogram plot with the ideal number of clusters as obtained from k-means plot (Figure 18), the colours used to aid in differentiation of the clusters. This dendrogram is for batch D of the scanned samples taken from the amnesty bins placed at Glastonbury Festival 2011.

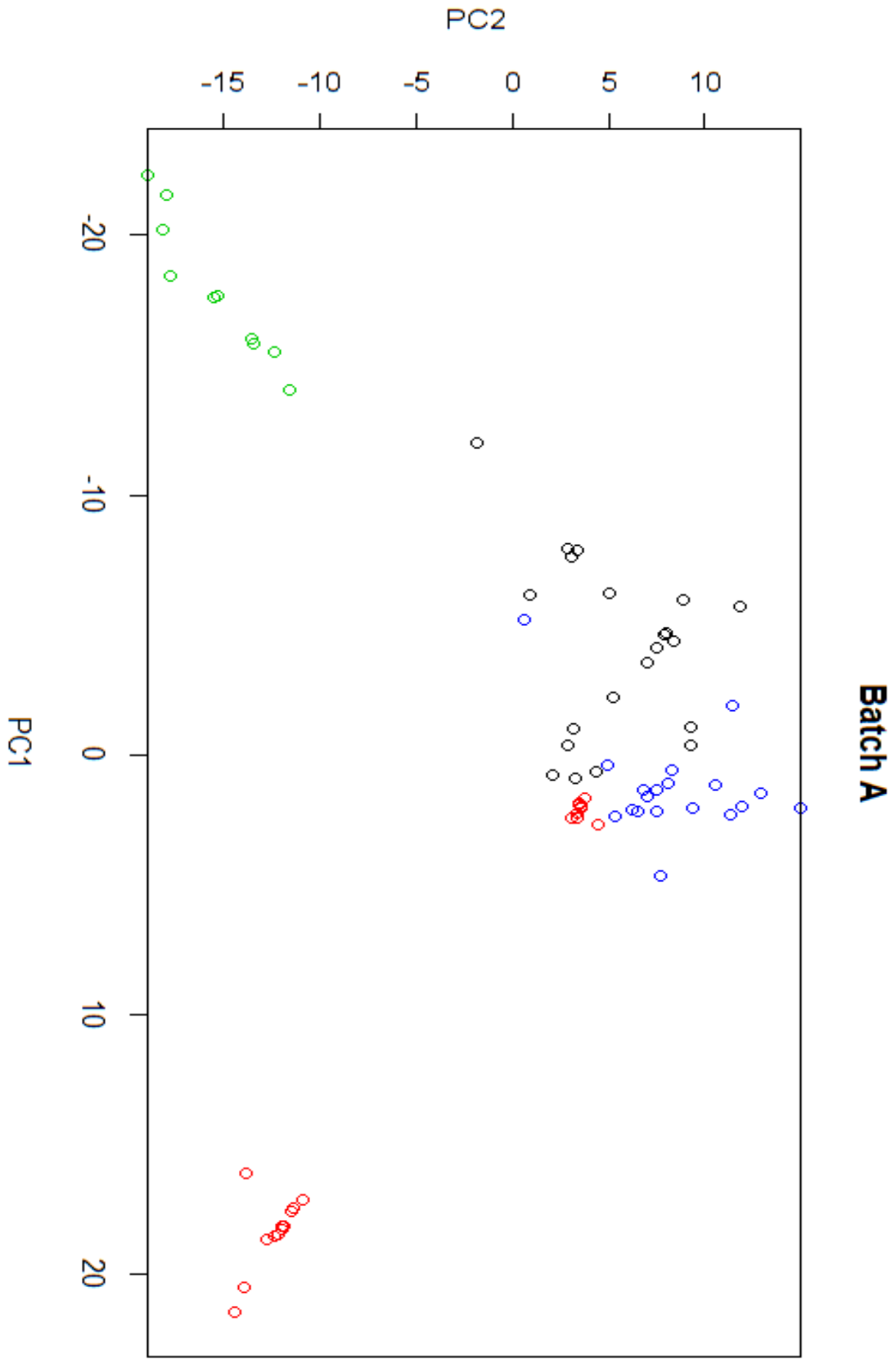


Figure 23 - PCA model of Batch A of the scanned samples taken from amnesty bins placed at the Glastonbury Festival 2011. Ideal cluster groups have been identified, with colours aiding to separate the clusters for user ease.

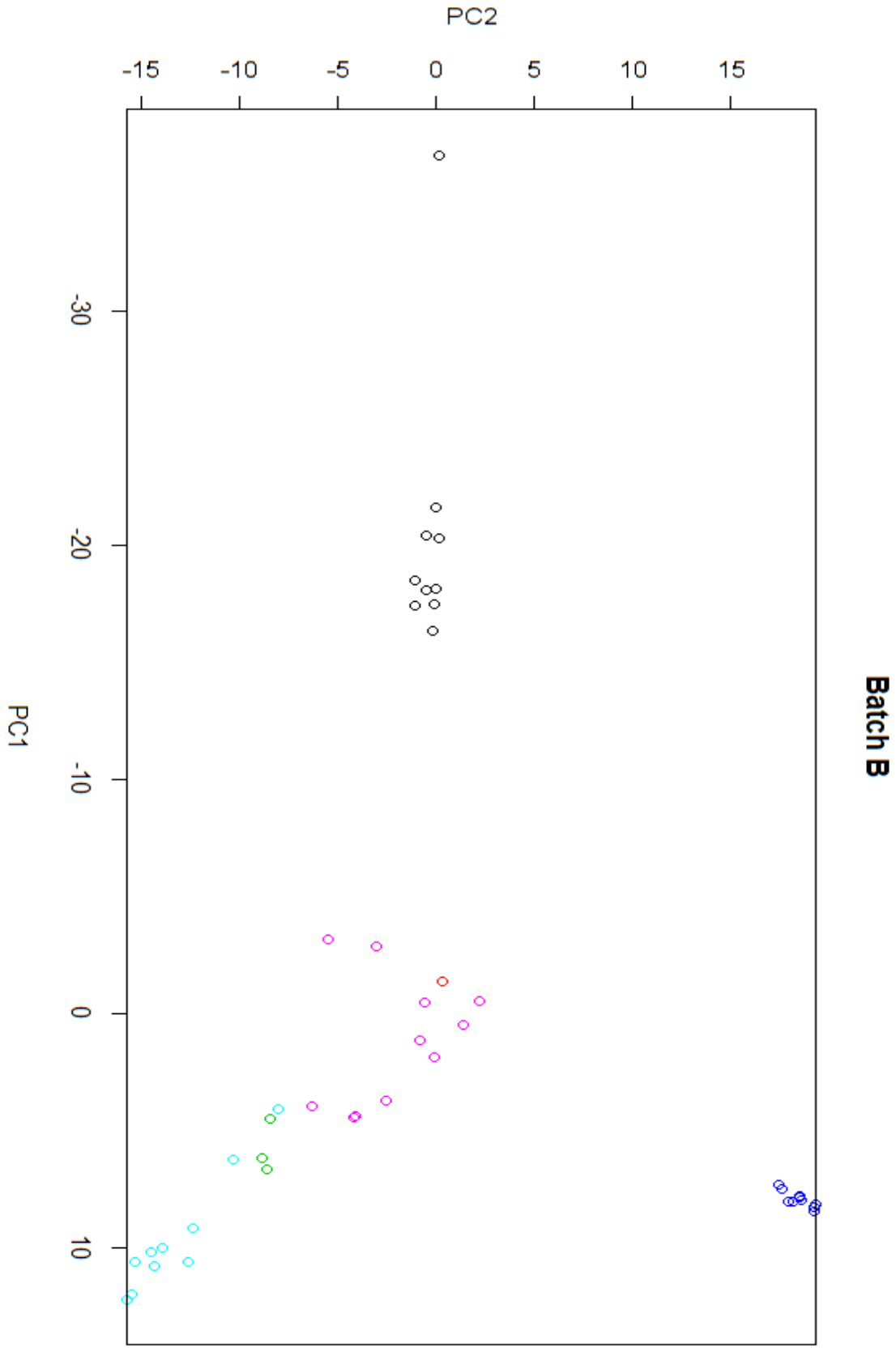


Figure 24 - PCA model of Batch B of the scanned samples taken from amnesty bins placed at the Glastonbury Festival 2011. Ideal cluster groups have been identified, with colours aiding to separate the clusters for user ease.

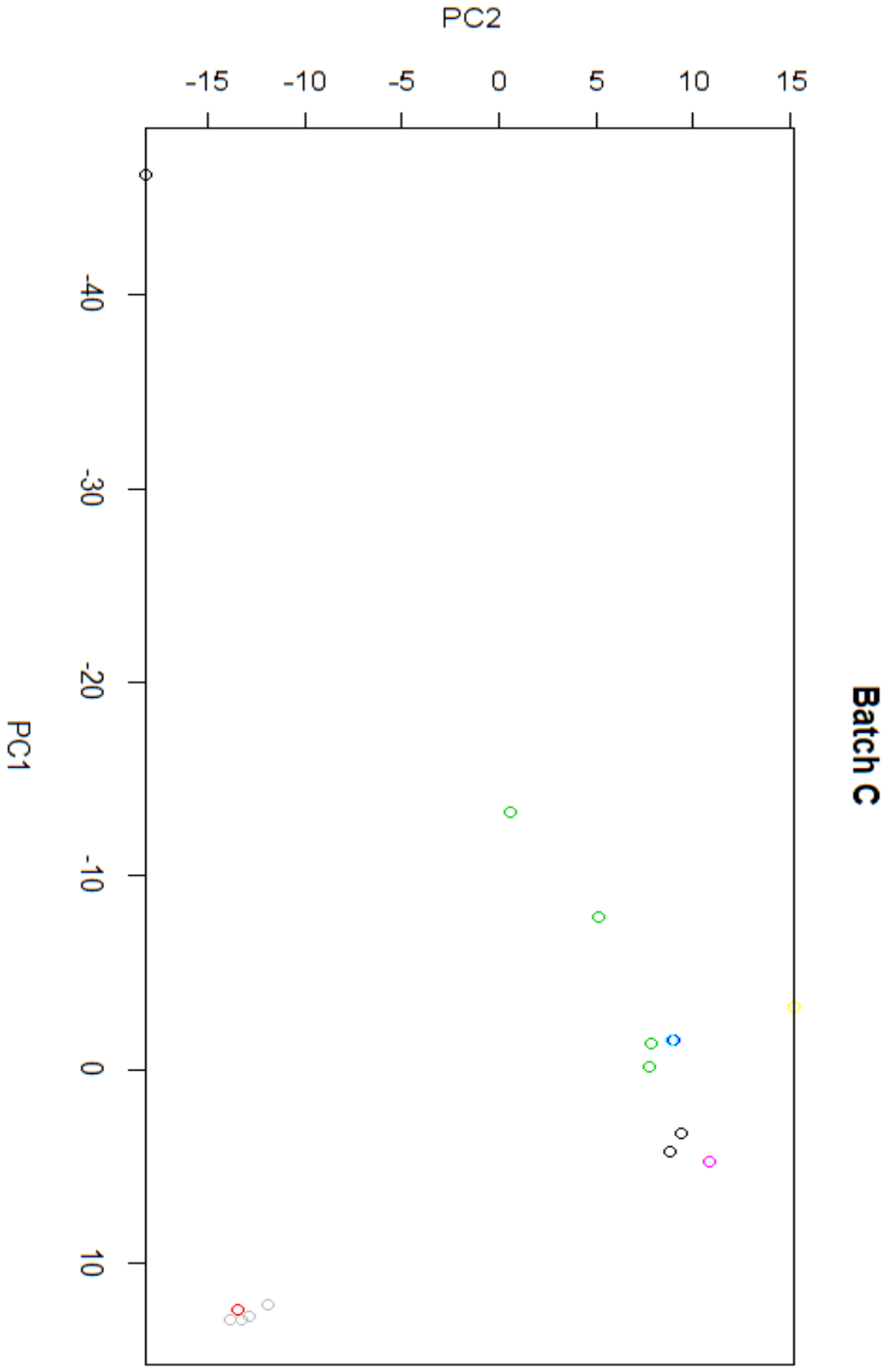


Figure 25 - PCA model of Batch C of the scanned samples taken from amnesty bins placed at the Glastonbury Festival 2011. Ideal cluster groups have been identified, with colours aiding to separate the clusters for user ease.

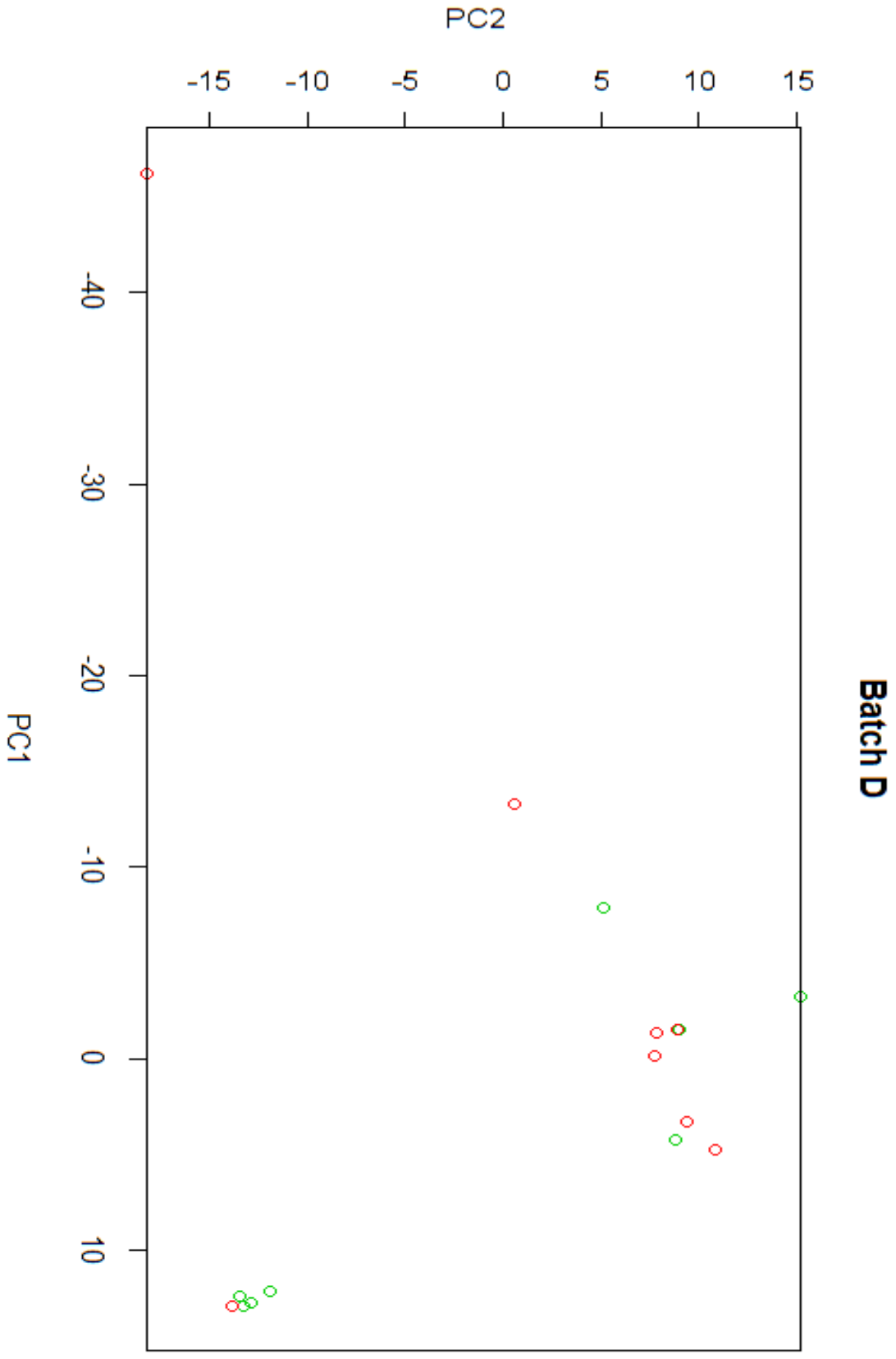


Figure 26 - PCA model of Batch D of the scanned samples taken from amnesty bins placed at the Glastonbury Festival 2011. Ideal cluster groups have been identified, with colours aiding to separate the clusters for user ease.

Unfortunately, these clusters do not correspond to alike clusters across the batches. To remedy this each of the batches were collated into an overall view. The same PCA, k-mean and dendrogram process took place, the results of which can be seen below in Figure 27 - 29.

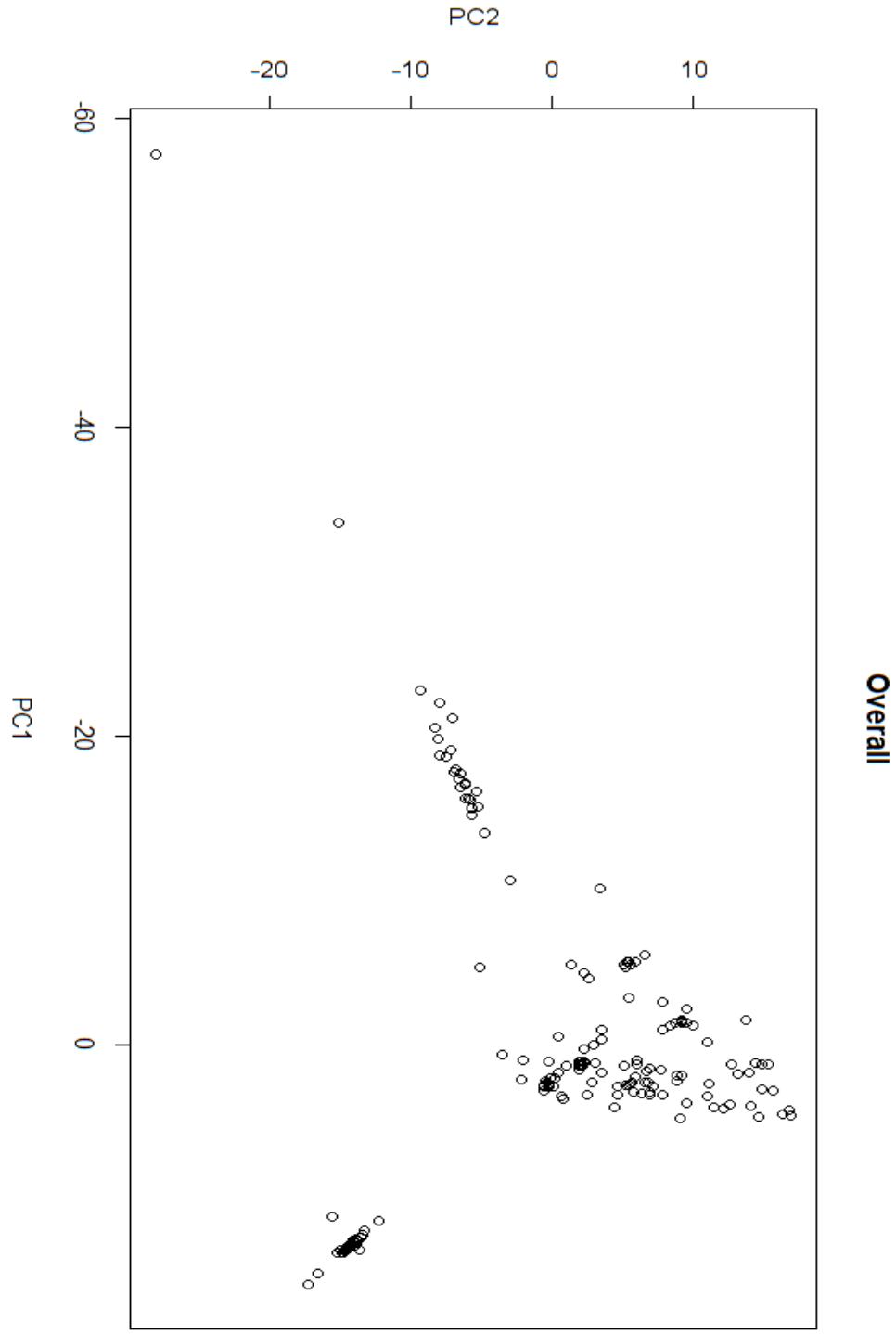


Figure 27 - PCA model for all batches of scanned samples taken from amnesty bins placed at the Glastonbury Festival 2011.

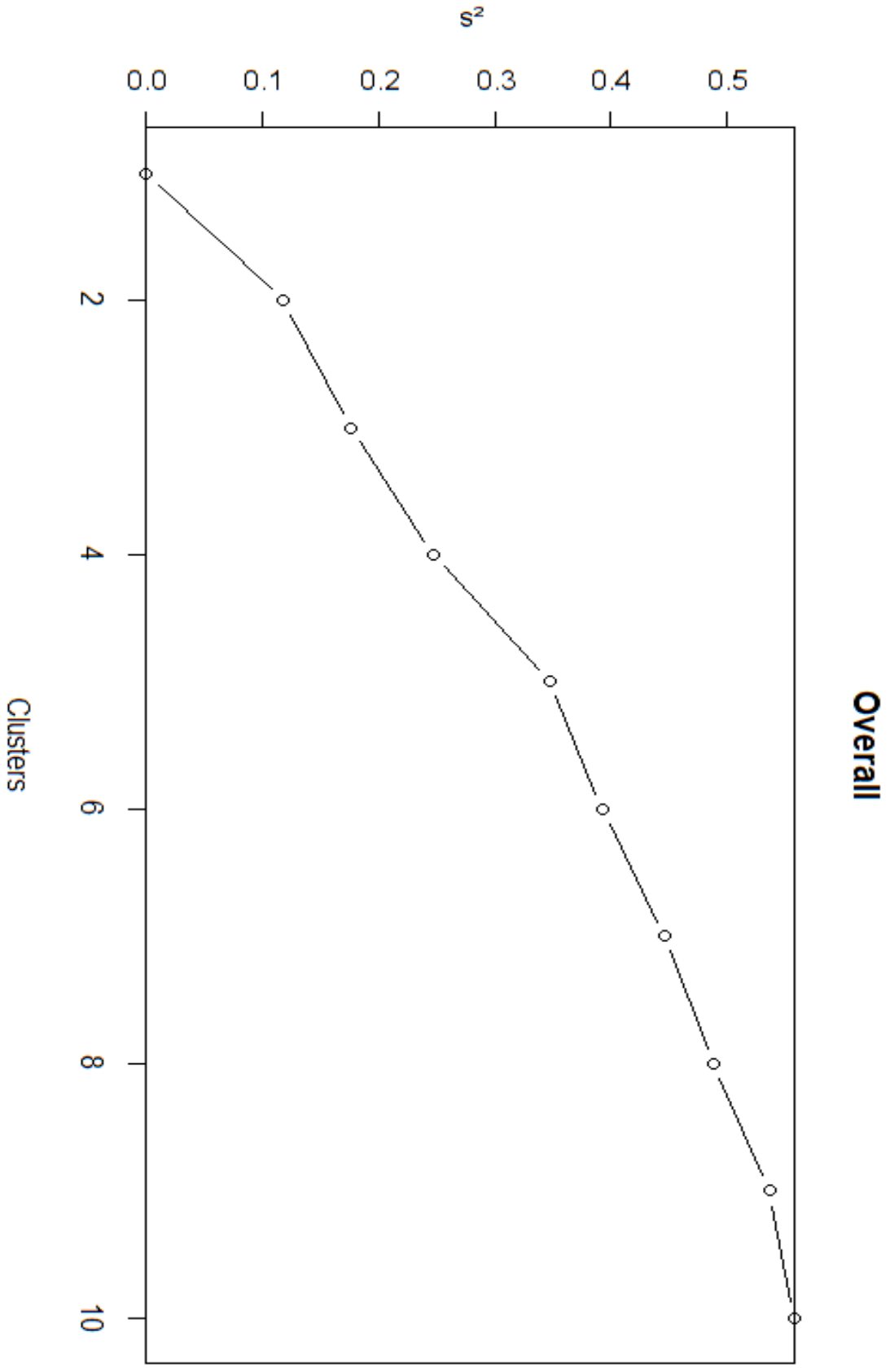


Figure 28 - k-means plot for all batches of scanned samples taken from amnesty bins placed at the Glastonbury Festival 2011.

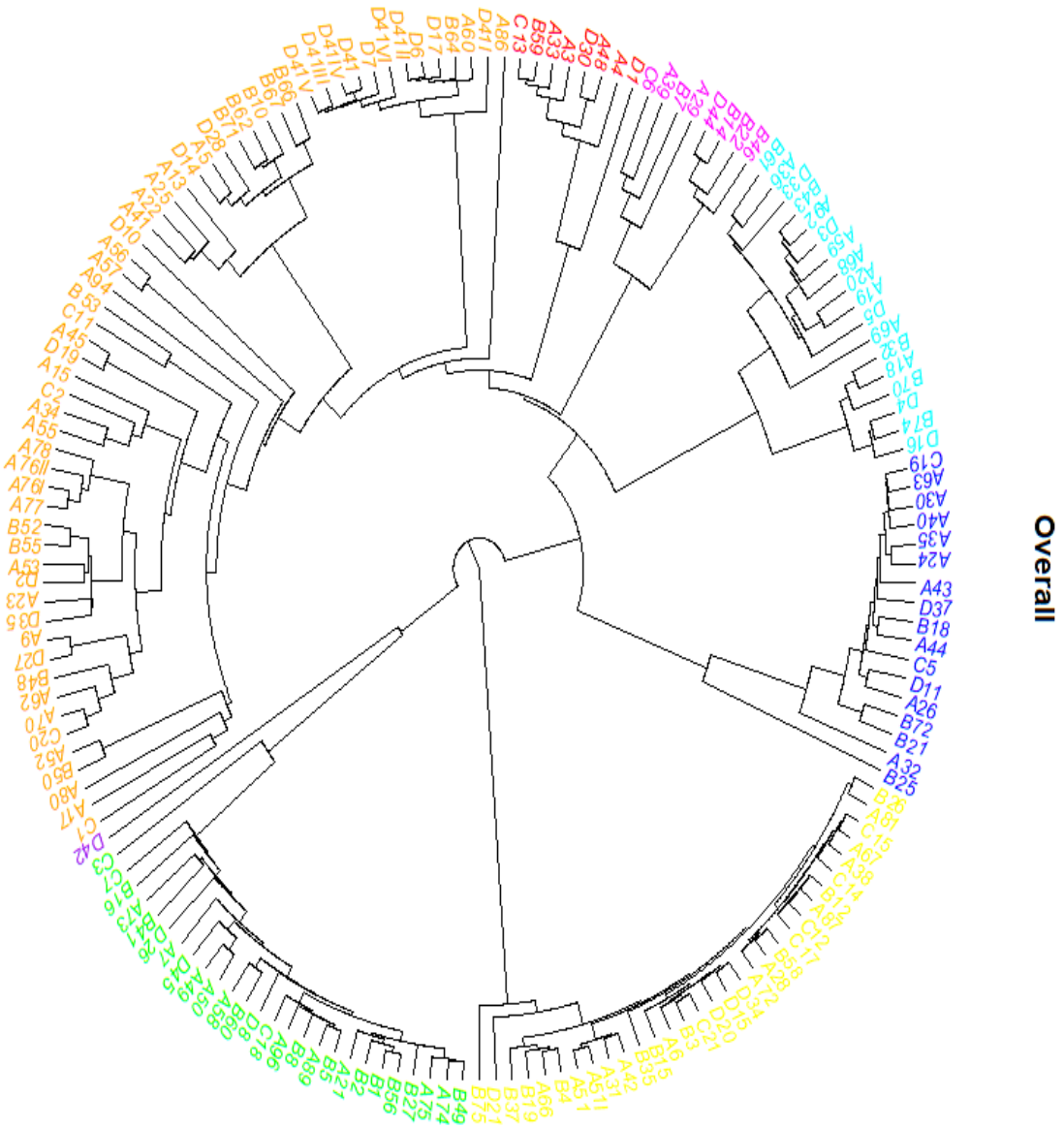


Figure 29 – Dendrogram plot for all batches of scanned samples taken from amnesty bins placed at the Glastonbury Festival 2011. k-means clustering has been applied with colour to aid in differing the clusters.

Once this statistical analysis had taken place, the spectra for each of the clustered groups were compared to see if the substances were alike. It should be noted that k-means and hierarchal clustering give an approximation to the ideal clusters however may not be able to distinguish some groups. This was the case with a few of the statistically clustered groups so manual clustering also took place to give the final groups for identification which takes place in the next chapter.

Raman Spectroscopy

Principles

Raman spectroscopy works on the basis of elastic and inelastic scattering of light when a monochromatic wave of light, ω_i interacts with a material system. Elastic scattering of light is known as the Rayleigh scattering. This is when the energy a photon gives to a material system is released back to the same energy state, i.e., V_0 to V_1, then back down to V_0. With inelastic scattering, the irradiating photon interacts with the material system, and the system will then vibrate. Depending on the type of vibration, depends whether something is Raman active. If the energy brings about, 'a change in polarisability', i.e., a symmetrical stretch of atoms in a bond, it is Raman active. (Whiffen, 1966)

In practice, the monochromatic wave of light used, ω_i is two coherent overlapping beams of light, ω_1 and ω_2; where $\omega_1 > \omega_2$. When either of these beams of light interact with a material system, the energy difference of the scattered photon, ω_s will arise to the situation known as Stokes-Raman or anti-Stokes-Raman scattering (Long, 2002). The source of the monochromatic light is often a laser in Raman spectroscopy, this is as it only emits light at a specific wavelength as is needed for Raman.

Equation 1 Stokes-Raman Scattering

$$\omega_s = \omega_2 - \omega_M.$$

Equation 2 anti-Stokes-Raman Scattering

$$\omega_s = \omega_1 + \omega_M.$$

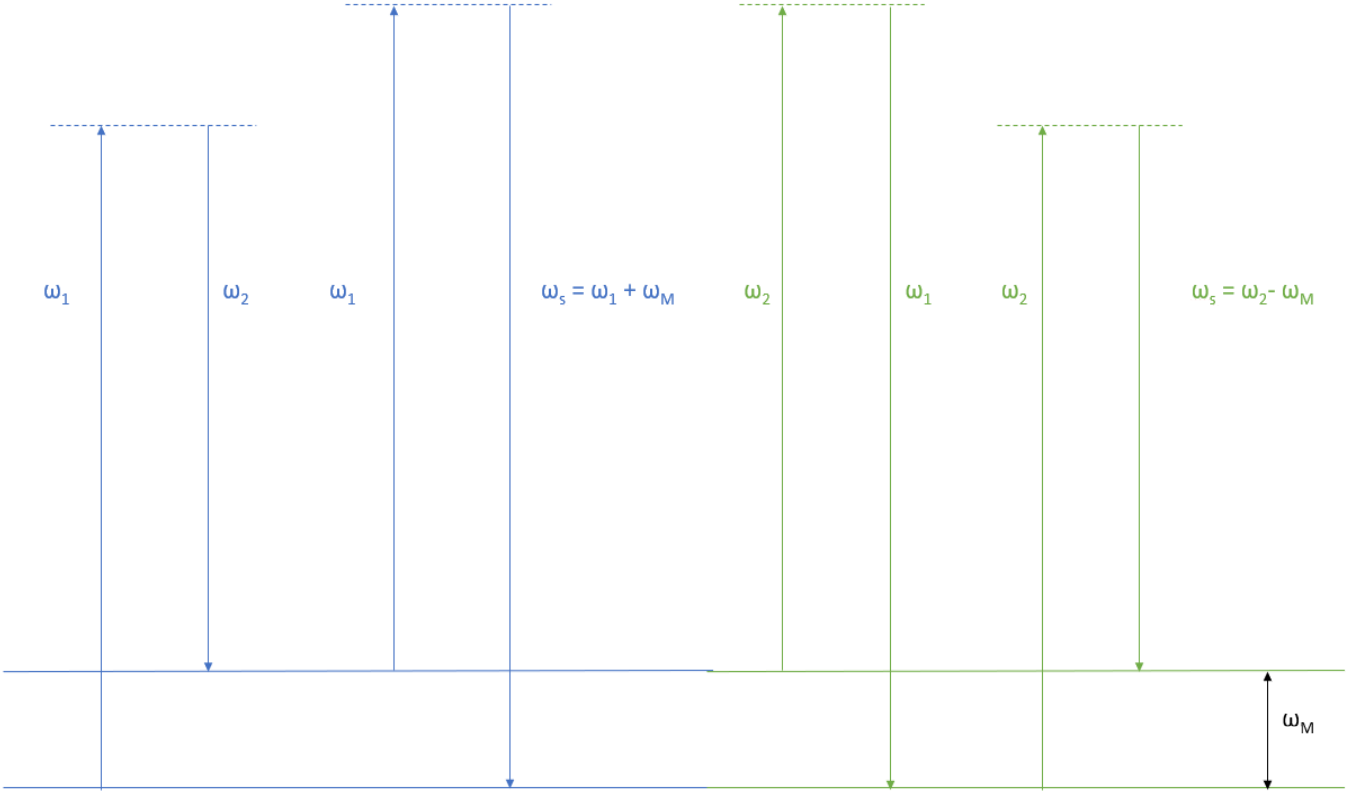


Figure 30 – Energy diagram showing the Raman effect. The blue (left) shows Stokes-Raman scattering in the molecule energy going from ground state without returning to ground state. The green (right) show anti-stokes-Raman scattering, showing how an excited molecule will return to ground state from an excited state.

These equations are summed up in the energy-level diagram above, Figure 30. This is the inelastic scattering of light and it is what we are concerned with when using the Stokes-Raman scattering effect in spectroscopy. This is as most molecules do not exist in an excited state before irradiating.

The spectra that are yielded during the experimental aspect are not expressed in terms of frequency, ω, but rather in wavenumber ῡ (unit cm^{-1}). To convert from frequency to wavenumber, apply equation 3;

Equation 3 Conversion from wavelength to wavenumber

$$\bar{\upsilon} = \frac{\omega}{2\pi c}$$

The Bruker BRAVO Duo Raman analyser emits an excitation laser at two different wavelengths as is the 'Duo' part of the BRAVO. These are at 700 and 1100nm and the two spectra are then stitched together to produce a spectrum across a greater range. It operates in the IR region of the electromagnetic spectrum. Unlike FTIR, the Raman works only at a specific wavelength of light, whereas FTIR will span the IR spectrum. Thus, Raman will yield results complimentary to IR but not exactly like such, due to the difference in the excitation wavelength. The difference also between Raman and IR spectroscopy is the way the energy will alter the molecule to cause a vibration. A symmetric stretch of a linear molecule will bring about a change in polarisability, which means it is Raman active. However, it does not induce dipole moment therefore is not IR active. An asymmetric stretch or bend will induce a dipole moment therefor is IR active, but not Raman active. Therefore, it is often said to be complimentary as one technique is able to analyse what the other may not (Whiffen, 1966).

The BRAVO does not have user programmable parameters, but it is published in the user manual the BRAVO will operate at < 100 mW, for both lasers, so is low power. Although it is not programmable, the machine has been specifically made to work through the packaging of the material it is scanning. There will be some interactions between the laser and the glass vials, however when seen in the spectra this is minimal.

Another benefit of the BRAVO is its reduction of fluorescence in the spectra, which in other spectra can skew the results. Fluorescence is a similar process to Raman scattering; however, it differs during the relaxation cycle of the phonon. Where in Raman scattering, the phonon will be excited to a virtual state and relaxed to a slightly higher energy level. In fluorescence, the irradiating photon will interact with the material system, and the phonon will be elevated to an energy level.

The phonon will then release energy before relaxation, this is called internal conversion. Fluorescence can overpower spectra so having a system which works to reduce fluorescence is ideal.

Experimental

After the data had been analysed and grouped as per chapter 2.2-4, the individual groups were then loaded into Spectragryph for identification and from this it was noted that the Bruker BRAVO Duo spectra that were yielded were reported in wavelength as opposed to Raman shift. The aforementioned, equation 3 was applied to each of the grouped data, then each batch within the groups were plotted as stacked spectra. This allows to see if there are any obvious differences between substances across batches. It also allowed for the functional groups to be identified and the substances subsequently identified.

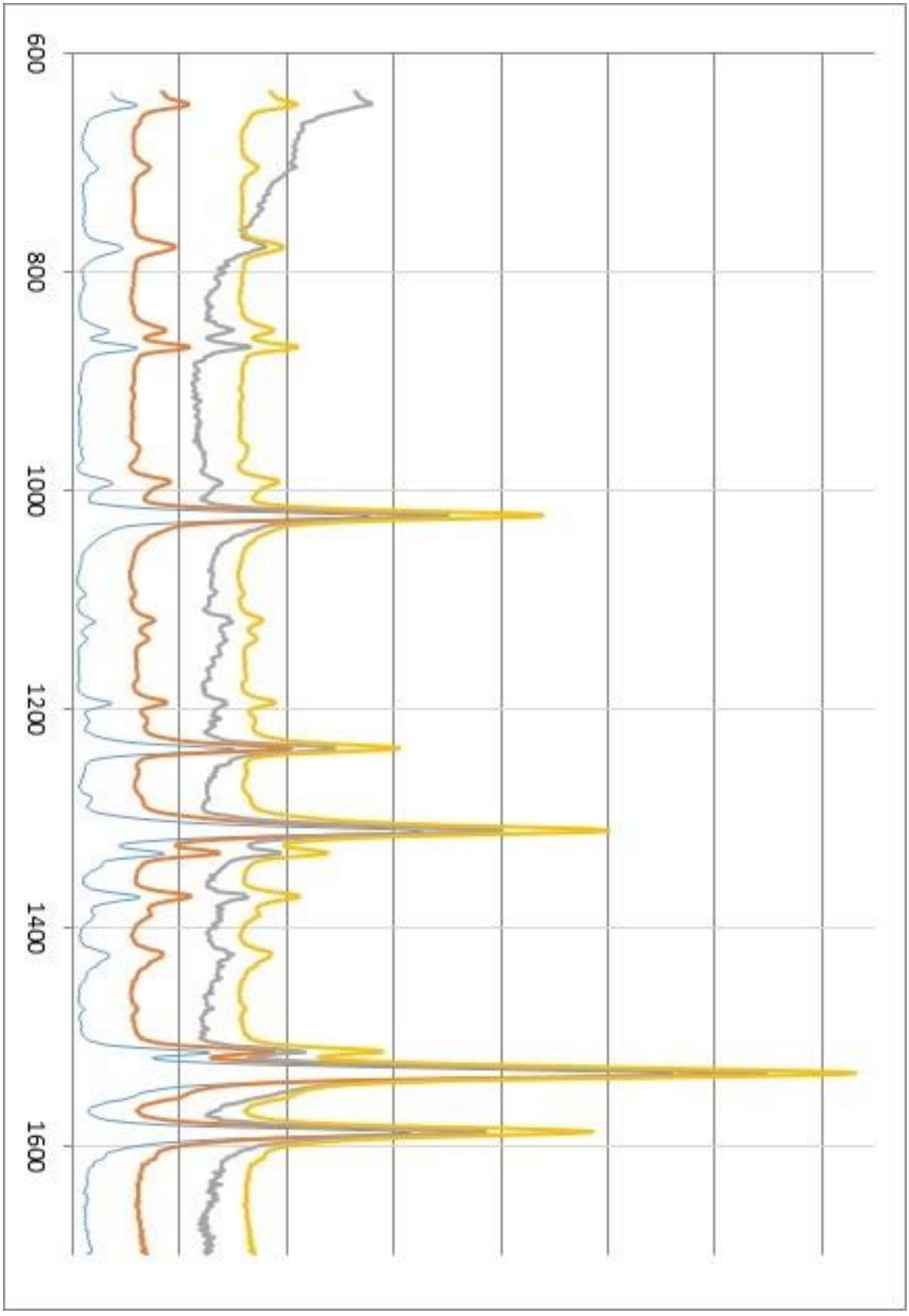


Figure 31 - Stacked spectra of identified cluster, now designated as group 1. All individual spectra for each of the batches for the identified group 1 were compiled to one spectrum per batch for ease of analysis. The blue line corresponds to batch A. The orange line corresponds to Batch B. The grey line corresponds to batch C. The yellow line corresponds to batch D.

Figure 31 shows the stacked spectra for group 1, the green coloured group from Figure 29. Major peaks are noted at 1600, 1280, 1275 and 860 cm^{-1}. These correspond to a 1^{o} amine, a methyl group, an aryl ketone and an ethyl ester. Therefore, it is postulated this spectrum is that of benzocaine, the structure of which is given in Figure 32.

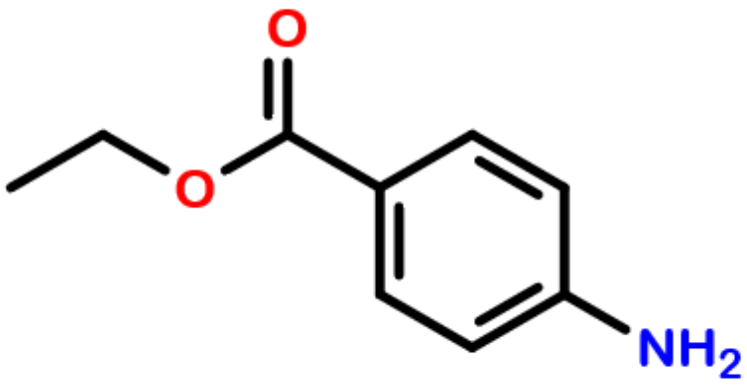


Figure 32- Chemical structure of Benzocaine

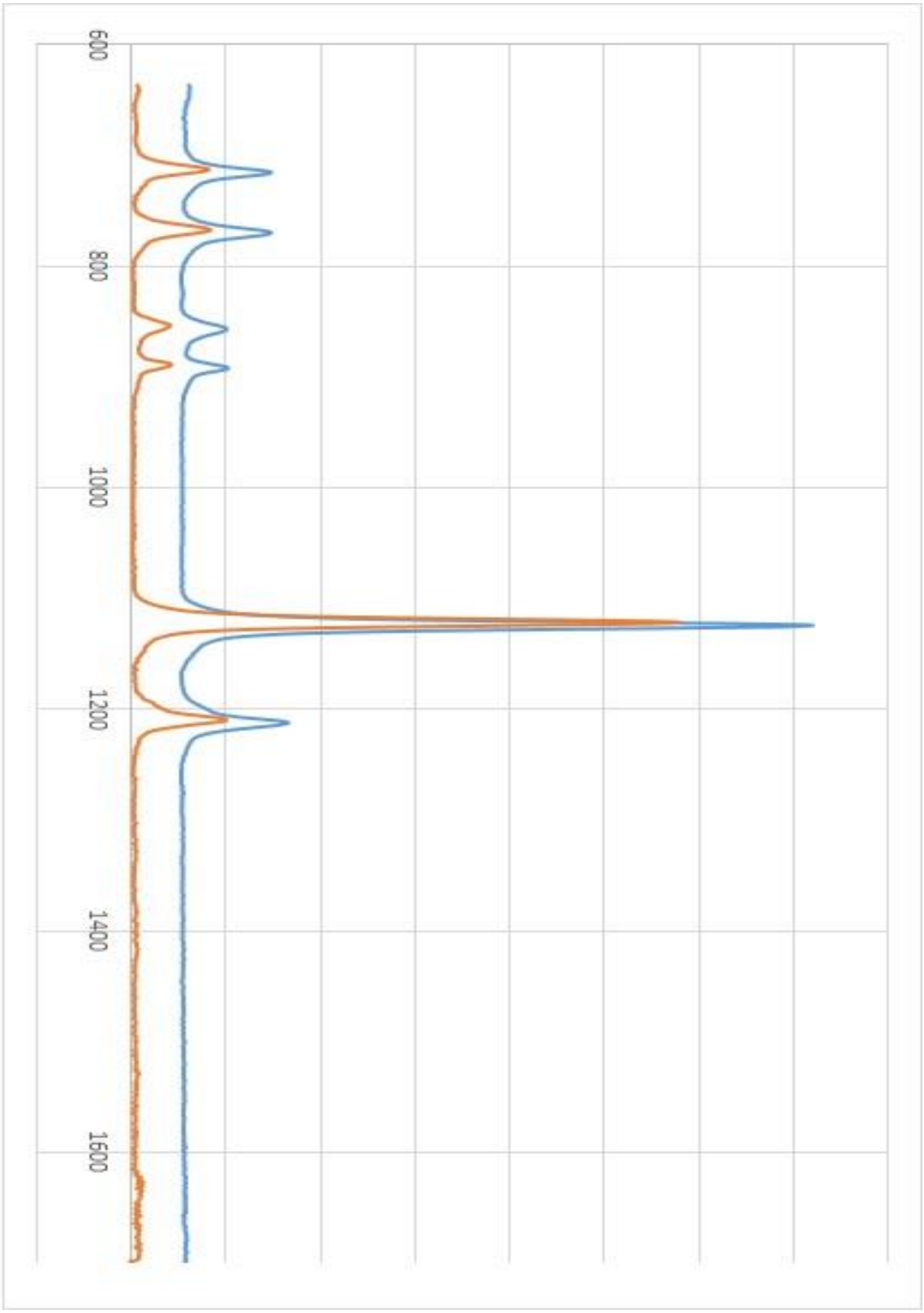


Figure 33 - Stacked spectra of identified cluster, now designated as group 2. All individual spectra for each of the batches for the identified group 2 were compiled to one spectrum per batch for ease of analysis. The orange line corresponds to batch A. The blue line corresponds to batch D.

Figure 33 shows the stacked spectra for group 2, the orange coloured group from the dendrogram in Figure 29. Major peaks can be seen at 715, 795, 920, 970, 1100 and 1236 cm^{-1}. These correspond with a 1,3- substituted benzene, aliphatic ether, an amine, an unsymmetrical benzene substitution, a halogenated aromatic and an ethyl join. Therefore, this substance is postulated to be 25I-NBOMe; the structure is given in Figure 34.

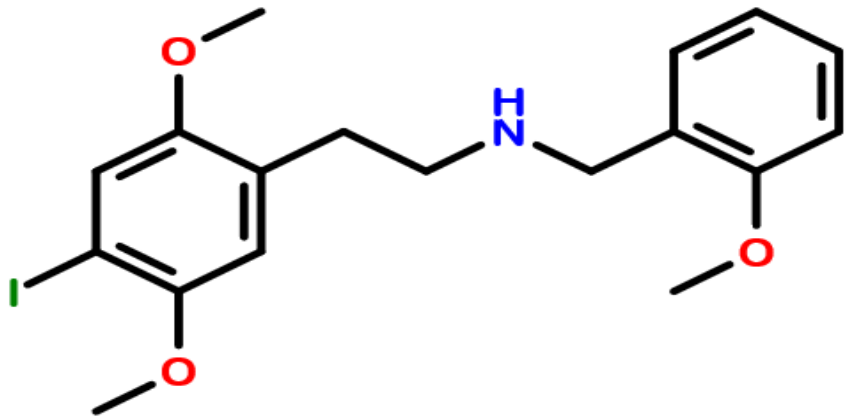


Figure 34 - Structure of 25I-NBOMe

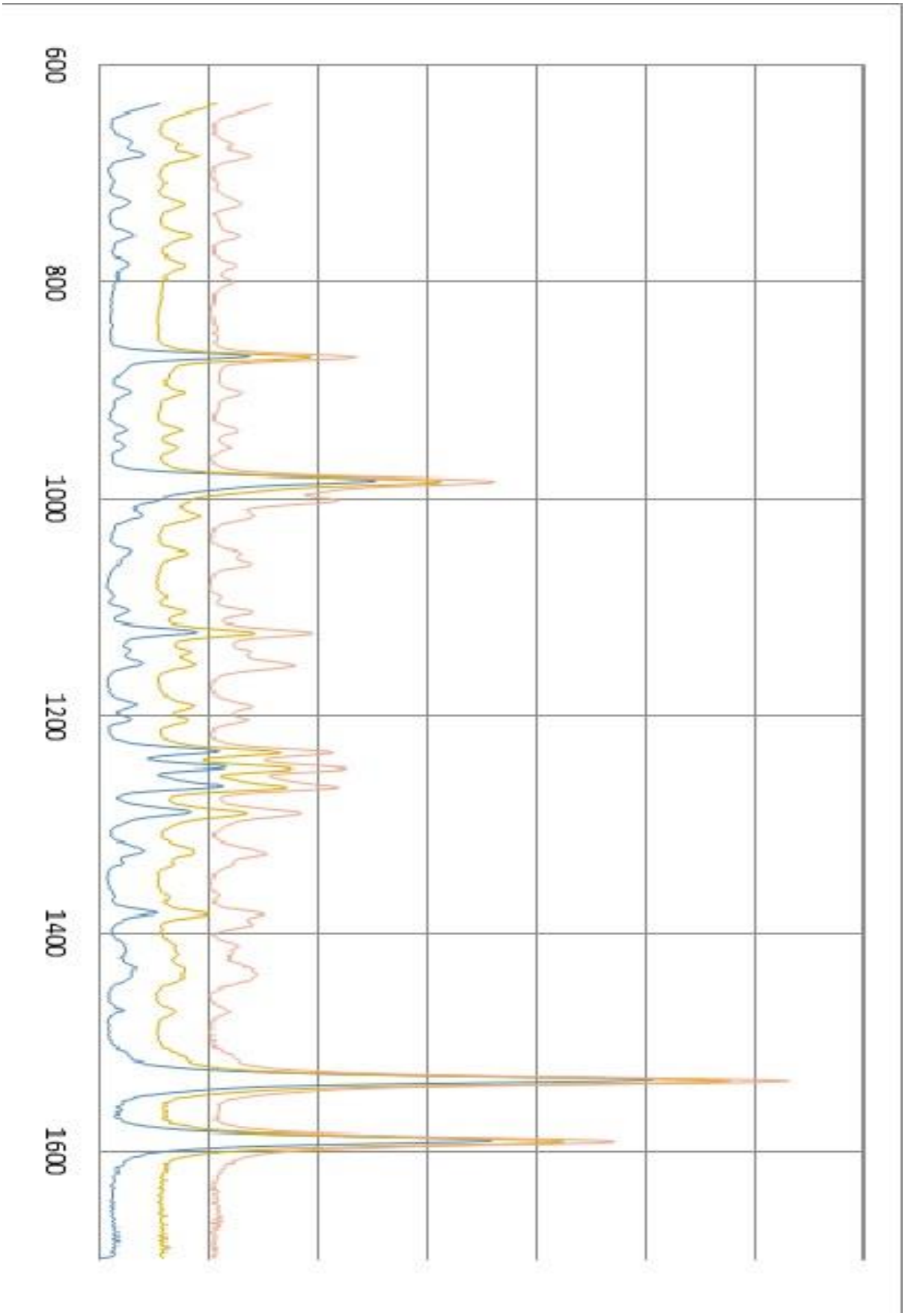


Figure 35 - Stacked spectra of identified cluster, now designated as group 3. All individual spectra for each of the batches for the identified group 3 were compiled to one spectrum per batch for ease of analysis. The blue line corresponds to batch A. The yellow line corresponds to batch B. The orange line corresponds to batch D.

Figure 35 shows the stacked spectra of group 3, the red group seen in the dendrogram of Figure 29. Major peaks are noted at 990, 1105, 1285, 1530 and 1530 cm^{-1}. This corresponds to an amine, a carbonyl, bisubstituted benzene, 1^{o} amine and isopropyl structure. It is therefore postulated the substance for these spectra is 4-methyl methcathinone, commonly known as mephedrone; the structure is given in Figure 36.

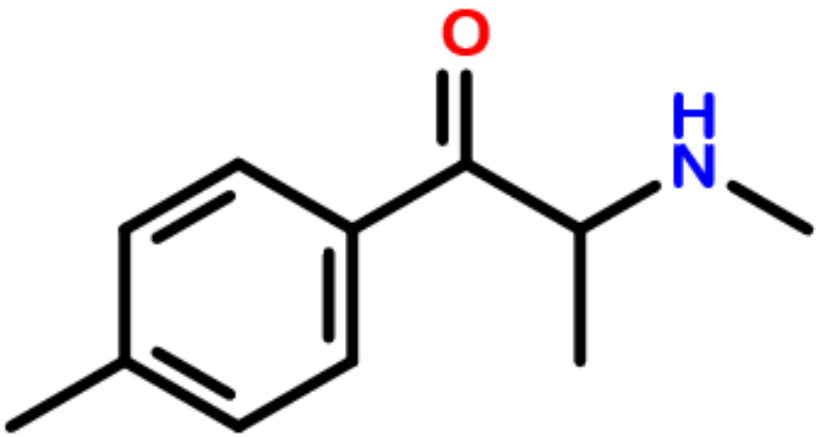


Figure 36 - Chemical structure of Mephedrone

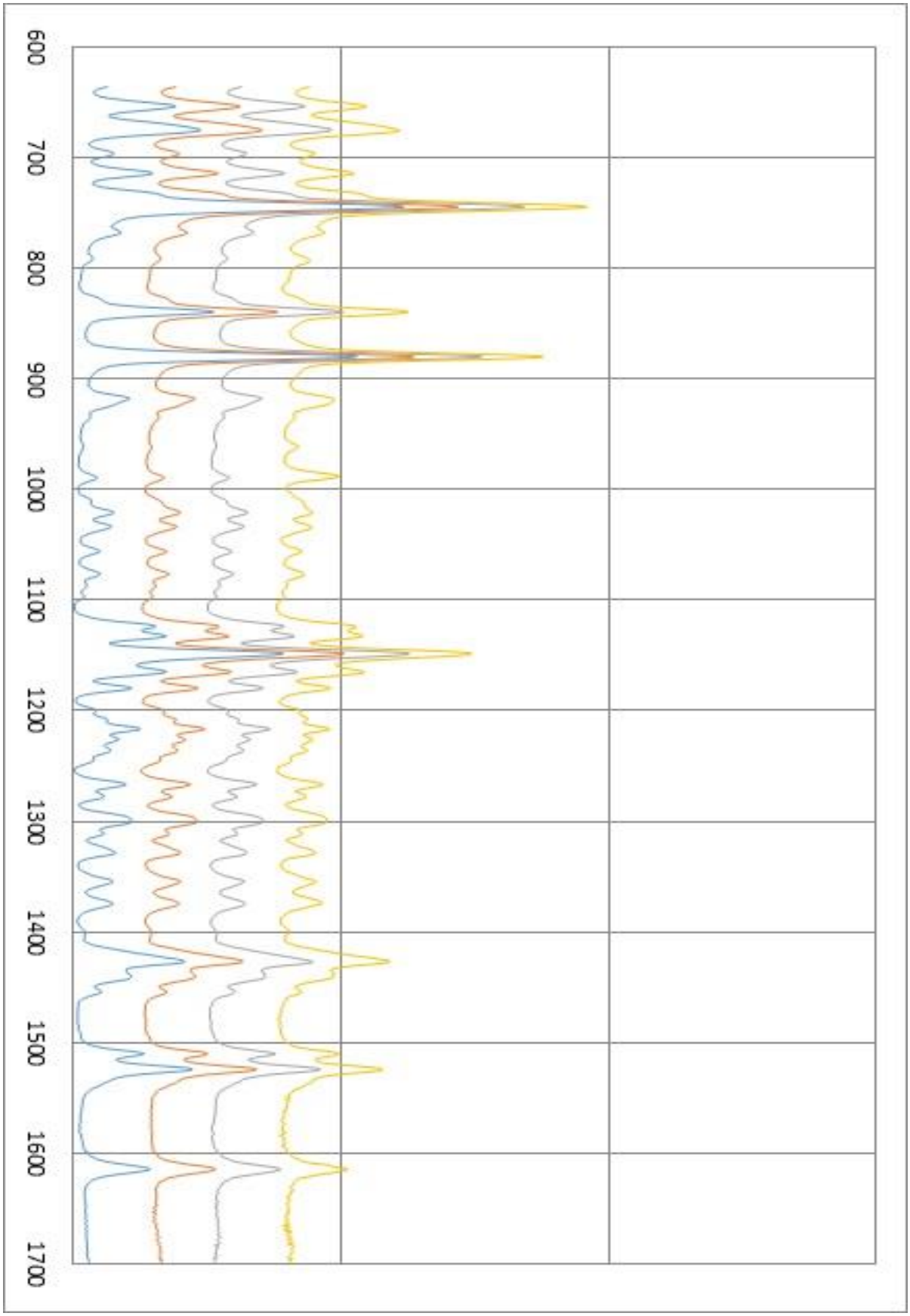


Figure 37 - Stacked spectra of identified cluster, now designated as group 4. All individual spectra for each of the batches for the identified group 4 were compiled to one spectrum per batch for ease of analysis. The blue line corresponds to batch A. The orange line corresponds to Batch B. The grey line corresponds to batch C. The yellow line corresponds to batch D.

Figure 37 shows the stacked spectra for group 4, the yellow group in the dendrogram seen in Figure 29. Major peaks are noted at 675, 850, 875, 1150, 1525 and 1610 cm^{-1}. These correspond with a bisubstituted benzene, a halo group, unsymmetrical benzene substitution, a methyl group and a 1^{o} amine. It is therefore postulated that this substance is ketamine; the structure is given in Figure 38.

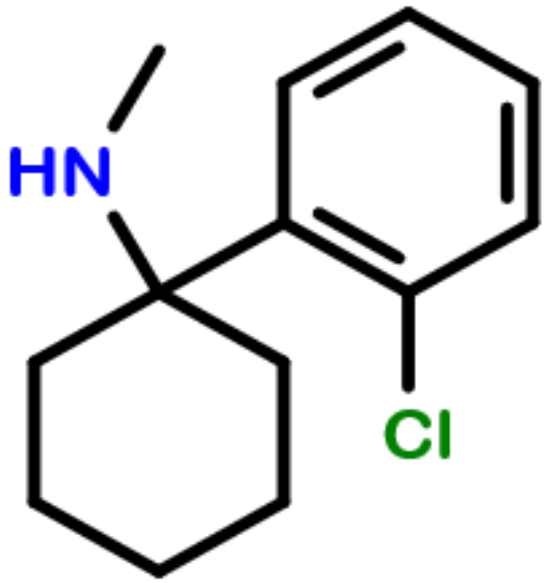


Figure 38 - Chemical structure of Ketamine

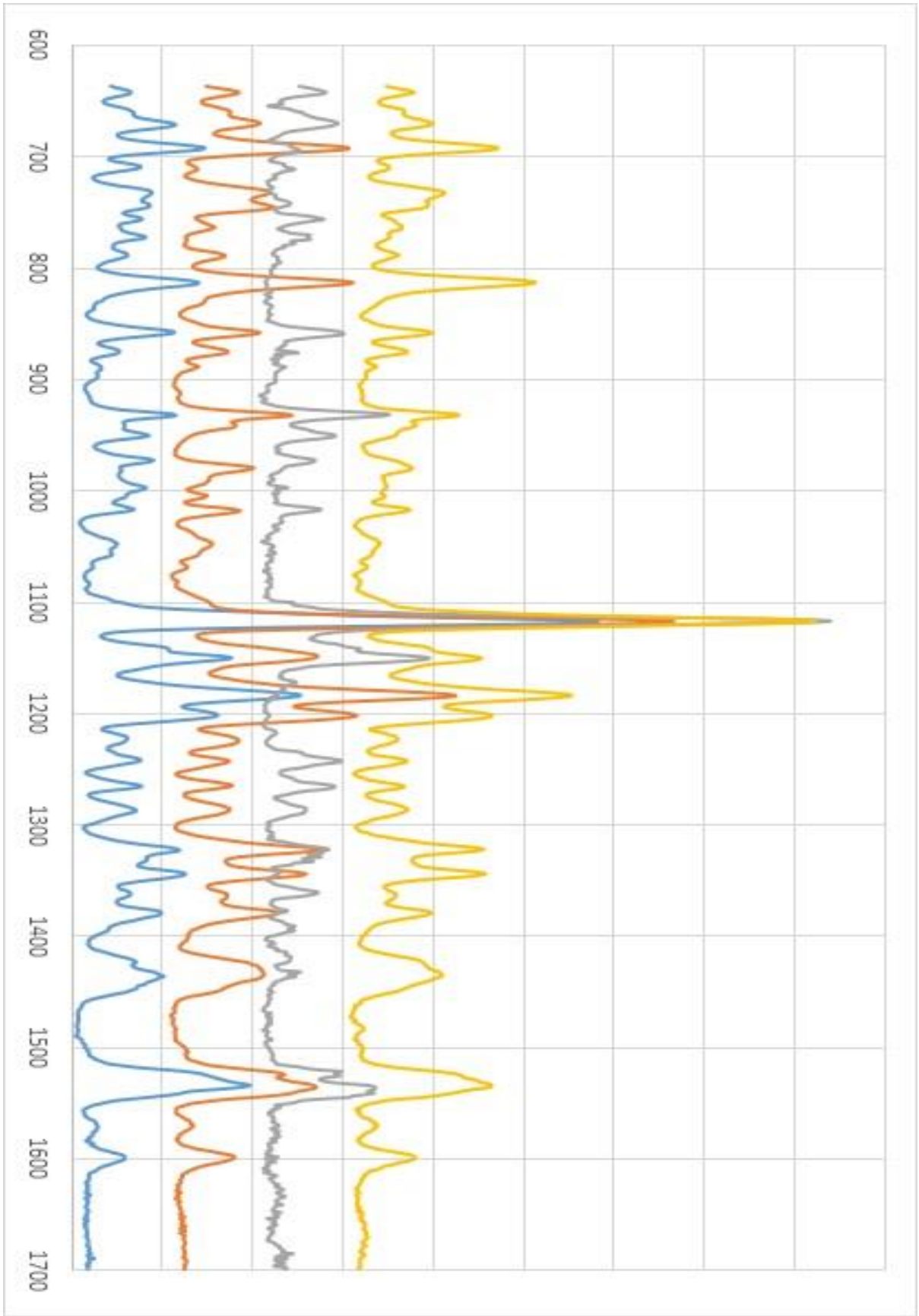


Figure 39 - Stacked spectra of identified cluster, now designated as group 5. All individual spectra for each of the batches for the identified group 5 were compiled to one spectrum per batch for ease of analysis. The blue line corresponds to batch A. The orange line corresponds to Batch B. The grey line corresponds to batch C. The yellow line corresponds to batch D.

Figure 39 shows the stacked spectra for group 5, the pink coloured group in the dendrogram of Figure 29. Major peaks are seen at 950, 1100 and 1550 cm^{-1}. These correspond with a primary alcohol, a butyl chain and a carboxylic acid. Therefore, it is postulated this substance is γ-Hydroxybutyric acid; the structure of which is given below in Figure 40.

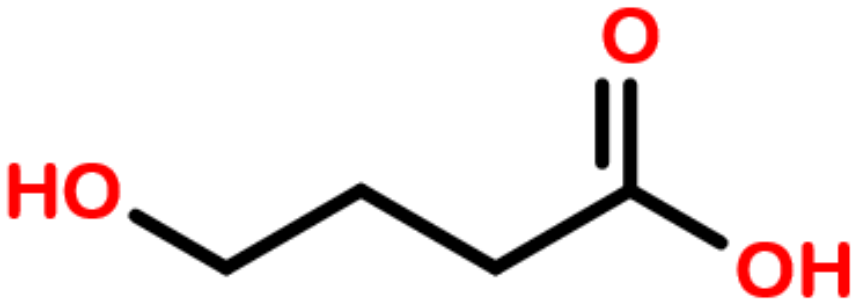


Figure 40 - Chemical structure of GHB

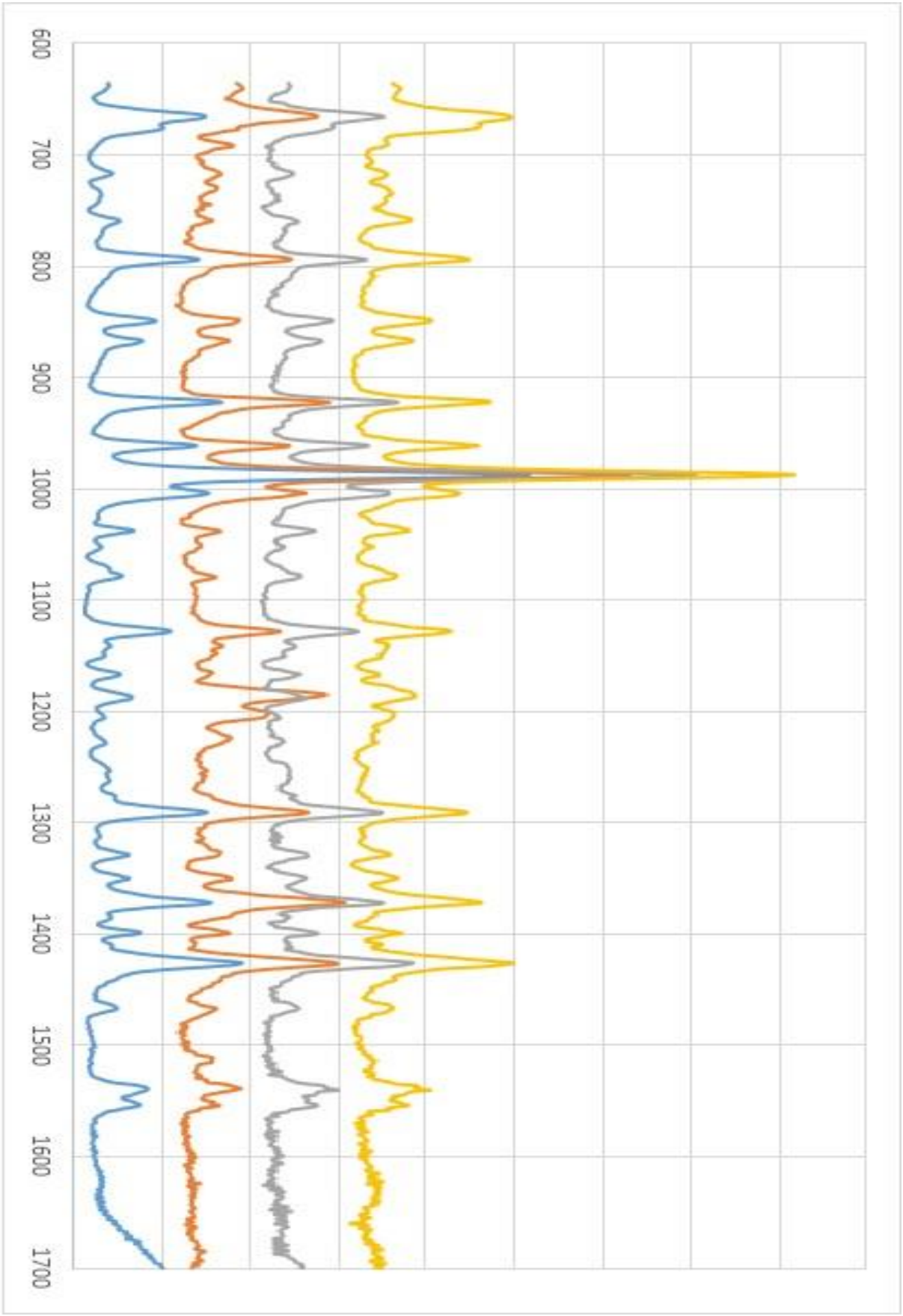


Figure 41 - Stacked spectra of identified cluster, now designated as group 6. All individual spectra for each of the batches for the identified substance in group 6 were compiled to one spectrum per batch for ease of analysis. The blue line corresponds to batch A. The orange line corresponds to Batch B. The grey line corresponds to batch C. The yellow line corresponds to batch D

Figure 41 shows the stacked spectra for group 6, the dark blue colour found in the dendrogram in Figure 29. Major peaks are noted at 790, 910, 980, 1125, 1370 and 1430 cm^{-1}. These correspond to a para-substitution, a methylene group, 1^{o} amine, an isopropyl group, a methyl group and a NH bend. It is therefore postulated that the substance is MDMA, better known as ecstasy; the structure of which is given below in Figure 42.

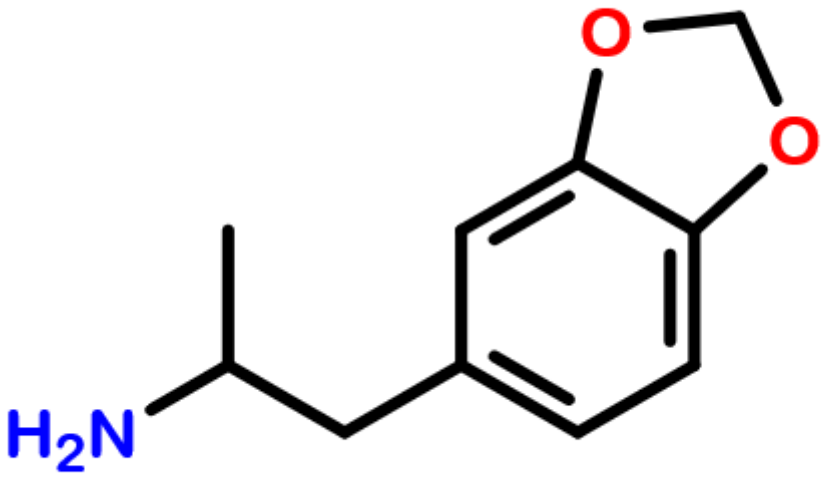


Figure 42 - Chemical structure of MDMA

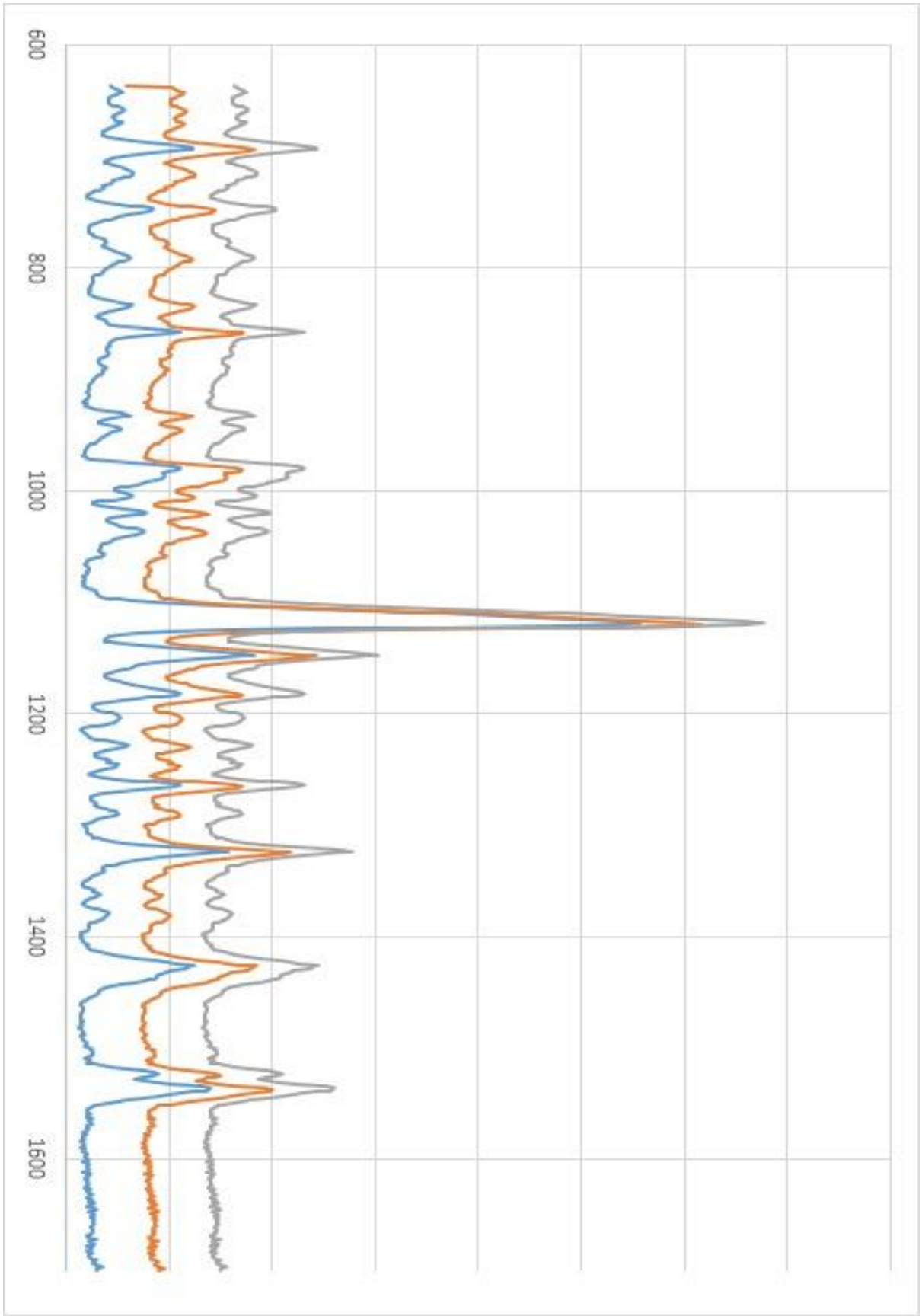


Figure 43 - Stacked spectra of identified cluster, now designated as group 7. All individual spectra for each of the batches for the identified substance in group 7 were compiled to one spectrum per batch for ease of analysis. The blue line corresponds to batch A. The orange line corresponds to Batch B. The grey line corresponds to batch C.

Figure 43 shows the stacked spectra of group 7, the light blue coloured group seen in the dendrogram from Figure 29. Major peaks are seen at 850, 1100, 1300, 1425 and 1525 cm^{-1}. These correspond with a substituted benzene, a methylene bridge, an isopropyl chain, a methyl group and an amine. Therefore, it is postulated this substance is an amphetamine, the structure of which is given in Figure 44.

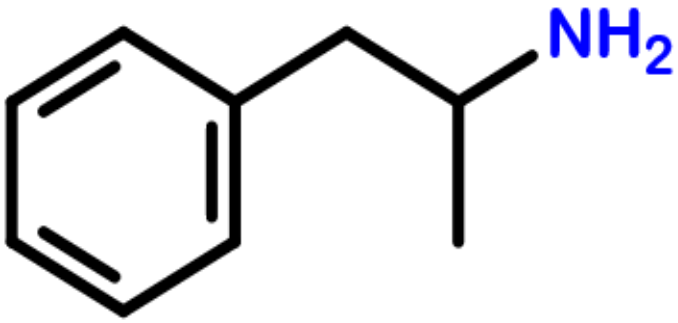


Figure 44 - Chemical structure of Amphetamine

To give a brief summary of the substances found during the experimental arm of this research, refer to table 2.

Table 2 - Summary of the substances identified from the cluster groups.

Group	Substance
1	Benzocaine
2	25I-NBOMe
3	Mephedrone (4-methyl methcathinone)
4	Ketamine
5	γ-Hydroxybutyric acid
6	MDMA (Ecstasy)
7	Amphetamine

Whilst the spectra seen from group 1 is of benzocaine, the physical properties of the some of the samples that were seen would indicate it is more likely to be that of freebase or 'crack' cocaine; 'street crack' has been known to been adulterated with other local anaesthetics (Lapachinske, S et al., 2015). It should be noted that Raman spectroscopy will only report one substance of a mixture, one which is 'more' Raman active, in this case whilst benzocaine is seen, it could be assumed based on the physical properties and the knowledge this is street dealt drugs, this is more than likely a mixture with the drug of abuse being freebase cocaine. It, however, should also be noted that during this time period it become fashionable to mix benzocaine with other NPS and sell this product as a cheaper alternative to cocaine (Legally High, 2013), therefore it could also be likely that some of these substances scanned could also be the imitation cocaine.

25I-NMBOMe, commonly known as 'n-bomb', or simply, '25I' is a synthetic hallucinogen, a substituted phenylethylamine (Expert Committee on Drug Dependence, 2014). At this time in 2011, 25I-NBOMe was not a controlled substance, however it was later advised by the ACMD that it be placed under a (temporary class drug order) TCDO (ACMD, 2013). It is currently a Class A drug; at the time it was collected it would have been an uncontrolled novel psychoactive substance.

Group 3 is 4-methyl methcathinone, more commonly known as 'mephedrone'. As a cathinone it is chemically related to amphetamine. Derived from the plant khat and chemically modified it acts as a stimulant. It was recommended by the ACMD in March 2010 that it be placed in the Class B of substances. By the time these samples were then collected, it would have been a classified drug under the Misuse of Drugs Act 1971.

Group 4 is ketamine, which has medicinal uses both in humans and veterinary practices. It is used to start and maintain sedation, however the first known implication to its recreational use, was an anecdotal reference in the 'The Fabulous Furry Freak Brothers' comic dated to the early 70s (Shelton, 2008). When used recreationally it brings about a dissociative effect.

Group 5 is γ-Hydroxybutyric acid (GHB), a GABAinergic drug used medically to treat seizure and narcolepsy. It has sedative like effects as it is an agonist of the GABA receptors, much like benzodiazepines or gabapentin. GHB has been a Class C drug in the UK since 2003 so would have been a long-standing classified drug by the point of collection.

Group 6 is 3,4-Methylenedioxymethamphetamine, MDMA, better known as 'ecstasy'. It is a substituted amphetamine having been popular since the 80s, notable use within in the clubbing scene was seen, as MDMA gave a boost of energy when taken (Anderson, 2014). It has been a classified drug in the UK since 1977, when an amendment to the Misuse of Drugs Act 1971 was enforced.

Group 7 is amphetamine, known as 'speed'. When taken it given a boost to energy and increases awareness. It has medical uses however these have been severely reduced due to the high likelihood of abuse. It has been illegal in the UK since the introduction of the Misuse of Drugs Act 1971.

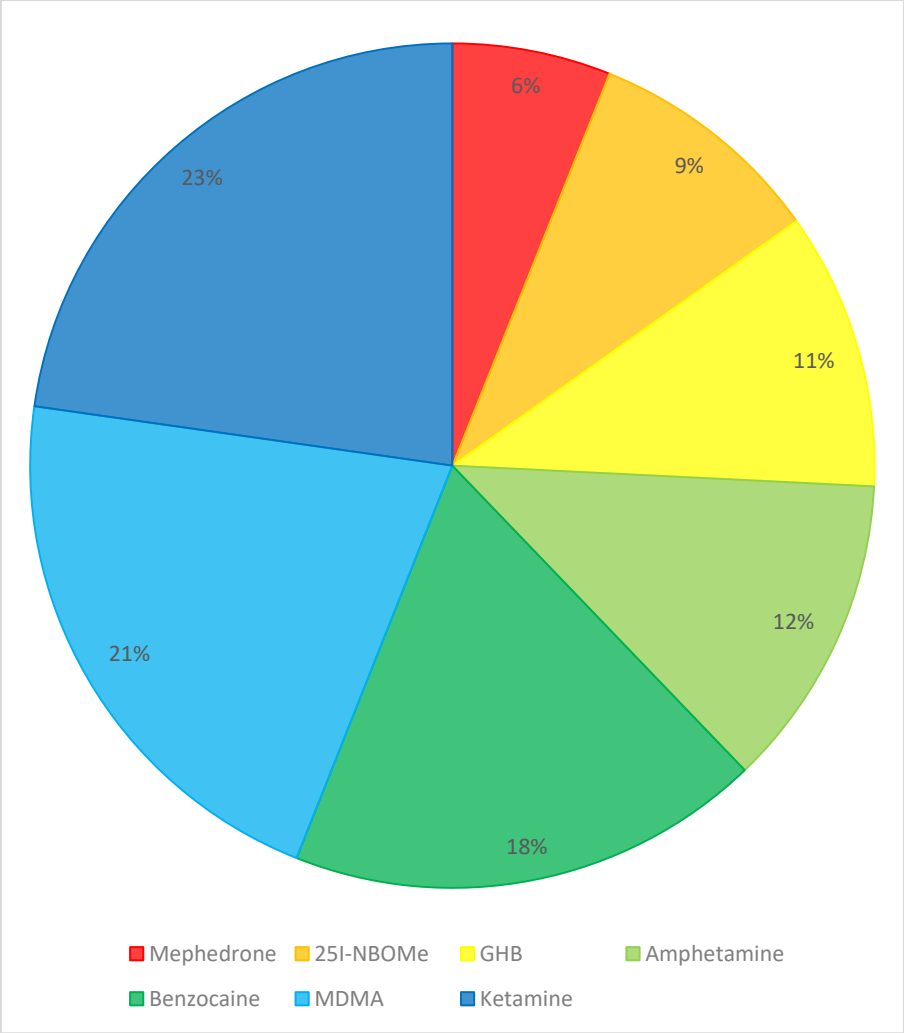


Figure 45 - Pie chart showing the proportion of each substance amongst all scanned substances of the samples taken from the amnesty bins placed at the Glastonbury festival 2011.

Figure 45 shows a pie chart, showing the percentages of how each substance is representative in the samples collected. It shows that the majority of use is shared with classical clubbing drugs MDMA and Ketamine. These samples were collected during the height of the NPS epidemic, so it would be expected there would be a higher number of NPS. It is worth noting that the average age of the Glastonbury attendee was 39 (Kienast, 2019), so this may show that this collection is not representative of the country as a whole at the time.

As is the nature with spectroscopy, when using correlation tables for the identification, it can often leave gaps in the interpretation. For a single wavenumber there may be many bands which it can correspond with.

Figure 46, is an example correlation table, where it can be seen at 540cm^{-1} (the red line), there can be many compounds which the spectral peak can correspond

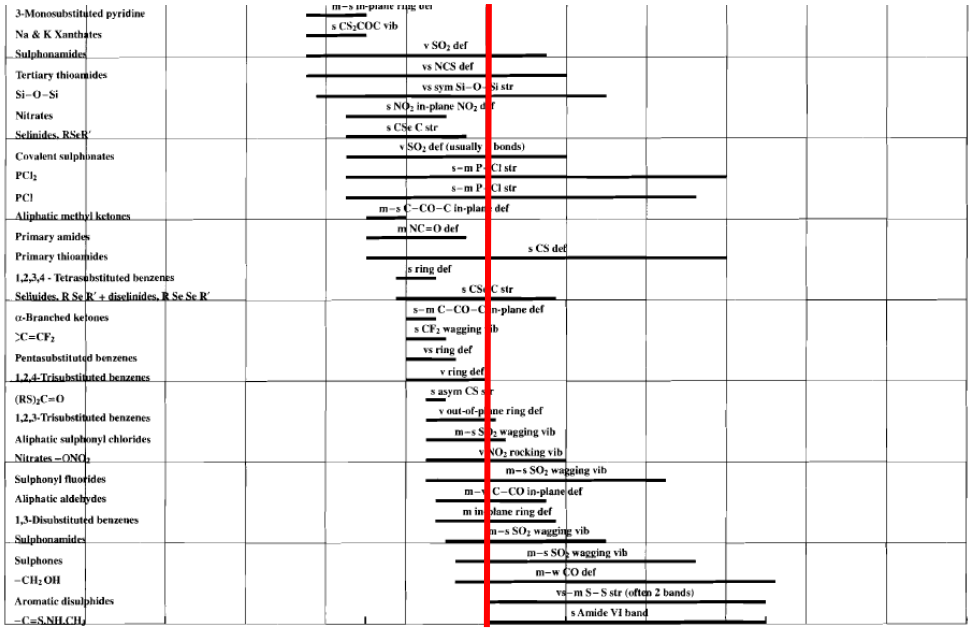


Figure 46 - Raman correlation table, with the red line highlighting 540cm^{-1}, showing multiple bands at this locus.

This can leave it down to the interpreter to make the best judgment call, based on any physical properties, or the chemistry it will most likely be made up of. Therefore, each of the substances identified in this section has been highlighted as being, postulated. To confirm the interpreted identification, control samples of high purity would be scanned, and the two spectra would be assessed for spectral likeness. This, however, could not take place during this research due limitations beyond control, so these postulations remain uncertified.

Raman spectroscopy will normally utilise a microscope for a pinpoint location on which the sample will be scanned. The sample is also often a thin film of material deposited onto a flat substrate, usually silicon. This can also be taken further, by enhancing the surface for scanning. By placing a thin film of gold nanoparticles, this can often enhance the spectra

yielded, this process being called Surface Enhanced Raman Spectroscopy (SERS). With handheld Raman, this pinpoint locus precision is not available, therefore there may be shift between the scanned surface between each scan.

During this research, there sample was scanned through the container, which was made of silica-based glass. This had little interaction, with minimal-to-no effect of the resulting spectra, however the no SERS could take place. For this study this is negligible, as the use of handheld Raman spectroscopy was for rapid-scanning, and to study the capability of handheld Raman for scanning of NPS.

Trends surrounding NPS in the period 2011 – 2015.

2011

This study is concerned with the change of trends within substance use, focussing on NPS. For this, the experimental arm of this study starts by analysing the contents of samples seized from the 2011 Glastonbury Festival. The Glastonbury Festival, the largest Greenfield festival in the world (Telegraph, 2017) is attended by hundreds-of-thousands of people yearly. The substances seized were from the 'amnesty bin' whereby festival attendees could safely dispose of any drug without any legal consequences of being in contact with that drug.

The analysis found that there were a mix of classical drugs and novel substances. Whilst this is not exhaustive of the full extent of the trends during 2011, it is a small population hoped to be somewhat representative. In addition to this information, data garnered from other sources, such as the EU early warning system, was used to give the best insight possible as to the trends emerging.

In 2010, the coalition government released a document to highlight its strategy for harm reduction. In which it indirectly used Wilson and Kelling's (1982), 'broken windows'

theory. This theory states that if there are visible signs of the area being dilapidated there will be a higher level of crime in that area.

The government pledged to make it so that the UK was no longer an appealing place for drug traffickers in an attempt to reduce the drug use in the UK, along with building communities back up so the population of the community felt there was other options than to form habits or addiction. In the same manifesto they stated that new powers would be introduced to control emerging NPS (Home Office, 2010).

It was then in 2011, the UK introduced a new parliamentary power, this being the Temporary Class Drug Order. This gave parliament the power to class a substance as a controlled drug, therefore being under the complete effects of the Misuse of Drugs Act 1971 (Home Office, 2011) for 12 months.

In 2011, the European Monitoring Centre for Drug and Drug Addiction (EMCDDA), ranked the UK as the 5th highest European country by mortality relating to drugs by population (EMCDDA, 2012). Whilst it can be difficult to compare this statistic across the member states, as each have is own criteria on inclusion, it does show the high number of DRD; 2,334, for the UK (ONS, 2012).

Also during this period, the Office for National Statistics (ONS), did not include a speciified group for inclusion into data for NPS, including DRD into exsisting group, such as as 'opioids', etc (ONS, 2012). The number given by the ONS is also those numbers which were mentioned as a complication in the death certificate. Therefore, the true number of NPS related deaths may not be fully disclosed as corners may not have been testing for NPS, or put it down to another drug.

2012

An explorative study from Scotland in 2012 highlighted the trends emerging - at least in Scotland, with regards to NPS. The study looked at drug related deaths (DRD), to see which drugs were most commonly seen, in special regards to NPS. The study noted that benzodiazepines and stimulants were highly used (McAuley, 2012).

This is in comparison with the experimental arm of this research, which shows that the likes of MDMA and amphetamine were highly used (33%). It was also worth noting the authors saw there was often a profile of mixing drugs with one another.

Koch et al. (2017), shows that users would often try and balance the up-down cycle with the use of benzodiazepines, alike to McAuley. By using benzodiazepines, it would make the down part of the cycle much easier on the user, however McAuley's research may be seeing that benzodiazepines were in fact being used to balance the up down cycle, not being the drug of choice for users.

An emerging trend in 2012 comes from the Office for National Statistics (ONS). The first dedicated section to NPS in the report on DRD appeared. This noted how there had been an increase in DRD implicated with NPS, from 29 to 52 (ONS, 2013). There was still a lack of a universal definition for NPS (ONS, EMCDDA 2013), with reports citing these substances as 'legal highs' (Wilkins and Sweetspur, 2013, Baumeister, et al., 2015, Freeman, et al., 2010), or, 'new psychoactive substances' (Larabi, et al., 2019, Kikura-Hanajiri, Kawamura and Goda, 2013), or then 'novel psychoactive substances (Wood and Dargan, 2013, Soussan and Kjellgren, 2016).

2013

The problem with NPS had gained national attention with the public by 2013, when the media had started to cover the problem. This is highlighted by the commission of multiple TV documentaries and news reports. Such as Cherry Healey reporting on BBC3, the 'youth-side' of BBC and 'Legally high' from Channel 4. Some of these TV documentaries noted how Trading Standards rules of no persons under 18 should be purchasing these substances and if the seller had any suspicion the buyer was going to consume it, the seller was obliged to refuse the sale.

Some sellers however didn't adhere to these standards (How To Get A Life, 2013), this is discussed further in chapter 5. In the documentary Legally High, Professor David Nutt explains how the market for NPS was made by the media. The quality of classic drugs had been going down, when pure, legal chemical came to the market. The media went into a frenzy and this spiral perpetuated the sale of NPS, as the media was offering front page information, people would take it as they saw these substances in the news and it was legal, therefore the media further reported on it (Legally High, 2013).

It was also in June 2013, the issues of the past years with NPS had been addressed in government. Ms Diana Johnson brought forward information regarding NPS such as how many substances had now been identified, how many had come to Britain and the effect it has had. She highlighted than in the two years since the government had the introduced temporary class drug orders, only one had been made with a 100 new NPS having come to

the market in the same two years (WH Deb 06 June 2013). It was then in July that the problem was address in the commons (HC Deb 15 July 2013).

2014

In 2014, the UK Government convened the, 'New Psychoactive Substances Review Expert Panel'. They had 6 months in which to review the situation surrounding the use and control of NPS and what would best be suited in the future to help protect the public. The review panel assessed how other countries had been affected and how they chose to deal with NPS, along with the evidence from within the UK to make an informed decision.

The review ultimately returned 5 options for the UK Government to restrict supply of these substances. These approaches included, analogue, neurochemical, general prohibition, full regulatory and restricted availability. The panel reached each of the recommendations by reviewing what other countries had done, and how successful it had worked in each country. For example, how the licensing system in New Zealand under the Psychoactive Substances Act 2013, whereby the sale of NPS is legal should it be licensed after human safety testing.

Ultimately, the UK Government chose to take an approach which made an amalgamation of the approaches, this leading to the Psychoactive Substances Bill, becoming the Psychoactive Substances Act 2016. The resulting legislation banned the production, importation and supply of NPS, but possession was not made illegal unless in a custodial setting, or it was possessed with the intent to supply.

2015

The issue with NPS had now started to take a toll on certain institutions within the UK, one of these being the NHS. Gilani reporting in 2016 of data collected in 2015, highlighted the struggle of a GP in treating a person who may have used NPS. She speaks of how treating somebody who is needs treatment for a classical drug of misuse, then the GP need only access ToxBase for guidelines, and prescribe the 'antidote'.

When a person presents who may have ingested a bit of 'Charly Sheen' or 'Magic Dragon', the case for treatment may not be as simple, for the patient may not know what the drug in the package is, and even if the packet says it is one thing, it is not always guaranteed to be that substance. In aid to try and combat this, The Novel Psychoactive Treatment UK Network (NEPTUNE), was founded in 2015 with the aim to give effective advice on the clinical management of patient who had taken NPS. They provided a comprehensive guide to the management of patients, and who the patients may be. They also go in-depth about the classes of substances most likely to encounter and how to effectively support those who may have taken them.

By 2015, drug related deaths - with NPS implicated, had risen from 82 in 2014 to 114 in 2015 (ONS, 2016). The ONS also reported that of the 114 death, 25 of those were from substances which at the time were legal. (ONS, 2016). This highlights the need for intervention, with people either assuming they're safe because these substances are legal, or they do not know the detrimental effect many of these substances have due to the lack of testing and authorisation of safety.

Government Responses

Whilst the Psychoactive Substances Act 2016 was pivotal in controlling NPS, it was not the first control measure implemented by the Government. As previously mentioned, the Government introduced the 'Temporary Class Drug Order'. This allowed for substances that posed a risk to public health, that were not previously covered by the Misuse of Drug Act

1971 to be banned (Misuse of Drugs Act, 1971, Ch. 2, s.2A). This power was given as an amendment to the Misuse of Drugs Act 1971 in 2010. It was upon the recommendation of the Advisory Council on the Misuse of Drugs (ACMD), that a substance should be banned. They made numerous recommendations for different substances to be banned, such as the NBOMe family and APB isomers to be banned (ACMD, 2013).

Once a substance was banned under a TCDO, it was then treated as a controlled drug under the Misuse of Drugs Act. After the introduction of the Psychoactive Substances Act 2016, TCDO fell out of favour; this was two-fold. First there is now a duality with the two Acts, substances not controlled under the Misuse of Drugs Act are now often controlled by the Psychoactive Substances Act, and so a TCDO is no longer needed to control these substances. Secondly, substances controlled by a TCDO are controlled by the Misuse of Drugs Act 1971 and therefore any psychoactive substance under a TCDO found in a custodial setting cannot be tried under the Psychoactive Substances Act 2016. As it is not an offence to be in possession of a temporary class drug it is evident how this duality of the Acts is vital in understanding.

Prior to the Psychoactive Substances Act 2016, there were multiple regulations in place from different sources, which were in place to ensure the safety of the buyer was maintained. These included, the Intoxicating Substances (Supply) Act 1985, the General Product Safety Regulations 2005 (GPSR) and Consumer Protection from Unfair Trading Regulations 2008 (CPUTR).

As aforementioned, one of the controls that superseded the Psychoactive Substances Act 2016 was the Intoxicating Substances Act 1985. Whereby it was “an offence for a person to supply or offer to supply a substance other than a controlled drug, to a person under the age of eighteen whom he knows, or has reasonable cause to believe, to be under that age” (Intoxicating Substance (Supply) Act 1985, Ch. 1, s. 1, ss. a). The effects of this in restricting

supply can be seen with a case study from September 2014. A 'head shop' – an outlet selling paraphernalia associated with tobacciana, was found to be selling NPS to children. It was made clear by the 16-year-olds who were sent into the shop they were underage and asked the proprietor how to consume the NPS.

The proprietor sold to the 16-year-old on each of the five occasions they were sent in undercover, the defendant received a three-month custodial sentence (suspended for two years), an 18-month supervision order and 120 hours of community service (Home Office, 2015). Along with home office undercover operations, the mass media also sent undercover operatives, which will be discussed later in this chapter.

An important control was derived from the protection of the consumer. Two key regulations to protect consumers in regard to NPS before the Psychoactive Substances Act 2016 were the General Product Safety Regulations 2005 (GPSR) and Consumer Protection from Unfair Trading Regulations 2008 (CPUTR). Whilst regulations are not as definitive as a law, they are still useful in protecting public health.

The GPSR aims to protect the consumer by ensuring that the products being sold are 'safe', i.e., being a substance, which has a minimal-to-no risk of causing ill-effects when the substance is used within the remit of normal use. Two major regulations within the GPSR are regulations 5 & 8, which places the onus of safety upon the producer and distributor respectively.

As is stated in regulation 5(1), "No producer shall place a product on the market unless the product is a safe product" (General Product Safety Regulations, 5(1), 2005). Regulation 8, states;

"(1) A distributor shall act with due care in order to help ensure compliance with the applicable safety requirements and in particular he—

(a) shall not expose or possess for supply or offer or agree to supply, or supply, a product to any person which he knows or should have presumed, on the basis of the information in his possession and as a professional, is a dangerous product; and

(b) shall, within the limits of his activities, participate in monitoring the safety of a product placed on the market, in particular by—

(i) passing on information on the risks posed by the product."

This is vital as the distributer being the head shop, the responsibility is down to the proprietor to ensure they are supplying a safe product and they are safeguarding the consumer by supplying the full safety associated with the product. As aforementioned, the mass media sent undercover operatives into head shops to see if the proprietor committed an offence under the Intoxicating Substances (Supply) Act 1985, as part of 'The Kyle Files' – a post watershed investigatory programme, an underage child was sent in to a head shop to test a range of safety precautions which should have been in place (The Kyle Files, 2015). Not only was the owner in breach of the Intoxicating Substances (Supply) Act 1985, he also failed to sufficiently explain the full dangers of taking NPS. This highlights how that not only head shops were not keeping within the safety precautions they should, but also how the media was exploring this issue and presenting it to a larger audience.

The main issue with prosecuting following a breach of regulations 5 & 8, is showing that to the criminal standard the producer/distributor had sold the substances knowing that the intent of the purchaser was to consume the product and that the product itself was dangerous. The issue with showing that the product was not dangerous is complex; with the vast nature of the products available and the ever-changing product range it would be difficult to trace the substance. Equally, had the producer/distributor sold it knowing the intent on the purchaser was not to consume it - but eventually did, the producer/distributer

knew the substance not to be dangerous if left untaken and could not be responsible as they sold it on the knowledge the person was not going to misuse it.

Another vital consumer protection given from the GSPR is the, 'requirement to mark'. The requirement to mark is given by regulation 12 of the GSPR.

If the local authority so deems a substance to be of danger to public health, the requirement to mark means the distributor must label the substance displaying the appropriate risks associated with the product. The flaw within this regulation, however, is the fact that no central government is ruling this. As it is down to the local jurisdiction to deem something as dangerous or not, one county may require to mark whereas another county may believe the substance to be safe.

An expansion upon regulation 8, which makes the distributer pass on all information regarding the safety of the product, regulation 13 is the 'requirement to warn'. This, like regulation 12, gives the local authority the power to deem a substance as dangerous and serve a notice to the distributer that they should be required to give a warning to the consumer this product has been deemed dangerous (General Product Safety Regulations 2005).

Further consumer protection is given from the Consumer Protection from Unfair Trading Regulations 2008 (CPUTR). The main points given from the CPUTR are to protect the consumer from the practices of deception i.e., the shop claiming to be 'endorsed' or 'authentic', when in fact there is no authorising body, for example. The packaging must not be misrepresentative of the contents, it cannot claim to be a substance it is not. The packaging may also not be deceptive in the branding in such a way that the packaging would make the consumer take the transactional decision they may not have under standard trading conditions (Consumer Protection from Unfair Trading Regulations, 5(2), 2008.)

Despite these laws and regulations in place to protect the public from dangerous substances, harm still continued to the public and in December 2013, Mr Norman Baker announced the commission of the New Psychoactive Substances Review Expert Panel, noting the need for a review to protect the public health (HC written statement, 12 December 2013).

Previous to the announcement of the review, there had been debate in the house of common on the best way to control these substances should a ban be implemented. The first suggestion by the member for Bassetlaw, John Mann was to implement a full ban on all psychoactive substances. The member for Cambridge, Dr Julian Huppert highlighted to the house, should an entire blanket ban be implemented then the coffee or tea the members had drank before coming to the house would be illegal as caffeine is a psychoactive substance (HC Deb, 11 November 2013). This is vital in showing the need for parliament to take advice on a nuanced area of expertise; this then led to Norman Baker convening the expert panel.

The recommendations of the panel have been previously discussed in chapter 4.4, the Psychoactive Substances Act was given its royal assent on 28 January 2016, with it becoming enforced on 26 May 2016. Whilst the act was successful in shutting down head shops and limiting accessibility to these substances, there were still criticisms to the act.

Stevens et al. (2015), highlighted the issue with the sentencing aspect of the bill. The sentencing powers at the time regarding drug cases, the judge used their discretion to impose a higher sentence on a drug deemed of 'higher harm'. With the Psychoactive Substances Bill, it is less likely for judges to understand which substance was of higher danger, therefore a proportional sentence was unlikely to happen.

In 2015, the ACMD highlighted an issue with the definition of psychoactive, within the bill. Whilst drugs similar in structure may have the same action, this cannot be proven without the in vitro study of psychoactivity (ACMD, 2015). Although, this was left ambiguous by lawmakers so that new substances could be banned without extensive testing.

Another criticism was the so-called 'displacement effect' which was seen in 2010 with mephedrone. Before the ban of mephedrone, it was seen that users of classified stimulants - such as MDMA and cocaine, started to change from an impure cut-down street product to stimulants like mephedrone, which were much more likely to be a pure sample (Measham et al., 2010). It was then feared that with the introduction of the Psychoactive Substances Act 2016, that this displacement effect would be even more pronounced (ACMD, 2015).

The criticisms facing the bill were mostly suppositions and based upon evidence of previously banned substances, the full extent of the effects would only be seen after the act was implemented.

Post-introduction of the Act

In the review by the Home Office as was required by the act, the Home Office says that the scene for the selling of these substances had changed; moving from shops to online selling (Home Office, 2018). With the digital revolution and the transition to the 'Information Age' (Castells, 1996) the populous of the internet has turned the drug scene from a street one to a virtual one (Orsolini et al, 2016). The question therefore is, was this change in the scene a natural progression or was it catalysed in the UK by the introduction of the Psychoactive Substances Act 2016?

The review states that it is difficult to measure but what is clear from the Crime Survey for England and Wales, the internet is still an important source of drugs for users (CSEW, 2018). The criticism is that by taking the NPS scene from the street to underground cause more harm as there was no regulation. As previously discussed in this chapter though, whilst there were some regulations in place, they were not entirely effective. In 2015, 114 deaths were recorded in relation with NPS; this raised to 123 deaths in 2016, but in 2017 this was reduced to 61 deaths (Office for National Statistics, 2017). This seems to be important as

when unregulated the deaths from NPS was rising, however once regulated it nearly halved (49.6% reduction).

In the Crime Survey for England and Wales, there was a reported reduction in the use of NPS amongst adults 18 – 59 years-old following the introduction of the Psychoactive Substances Act 2016. In 2015, use amongst the population was 1.1%, in 2016 this reduced to 0.6% and in 2017 further reduced to 0.5%, this is a reduction of 0.5% and 0.1% respectively year-to-year (CSWE, 2017). However, whilst this household survey has reported positive affects following the introduction of the act, there may not be all positive effects.

Addaction, a charity with a focus on aiding those with habitual use or addiction with substances, in 2017 released a report with a focal point on the health of young people, and their use of NPS. They had a self-submitted online survey for young people aged 16-25 to garner information about the use of NPS amongst this demographic. The survey took place in the autumn of 2016, so a few months after the introduction of the Psychoactive Substances Act 2016. The young people reported that the Psychoactive Substances Act 2016 had not deterred them from taking NPS, only that it made it harder to access and more expensive. They also reported as they now had to visit a dealer to get the NPS, they would also be more likely to get classical drugs of abuse at the same time. In a study of a Norfolk school, it was revealed that students in 2018 were still taking NPS. 8.7% of respondents had reported use of NPS, so this may support the findings of addiction (Roderick et al., 2018).

NPS are still being produced outside of the UK; designer benzodiazepines (BZD) have become increasingly popular (Zawliska and Wojcieszak, 2019). Whilst deaths still occur from the use of NPS (Koch et al., 2018), with this new influx of designer BZD having the Psychoactive Substances Act in place means that all designer BZD imported into the UK are immediately illegal. This means the UK Government is no longer having to ‘catch its tail’ to keep all these different compounds banned.

Alongside this is the previous attempt of sellers to circumvent the regulations was to label NPS as 'plant food' or such the like (Beharry and Gibbons, 2016). Following the introduction of the Psychoactive Substances Act 2016, there is no circumvention.
Such is the example of Phenibut, a medication in Russia, it is not scheduled in UK so is often labelled as a health supplement. As it is a known psychoactive substance, should a person import it as a health supplement they will be breaking the law. It is only illegal however, should a person import it, the possession of the substance is not, this will be discussed further in chapter 7.

Discussion

From this study, it can be concluded that the use of handheld Raman is possible to test samples of NPS. It appeared there was no masking of the sample's active ingredient by additives, when sampling NPS, as a pharmaceutically active ingredient appeared in all spectral groups. As previously mentioned, Raman is a surface-level technique, so will only yield results from the surface. If that means the additive is more Raman active that the active ingredient there will be masking of the samples active ingredient's spectrum. As a result, Raman can be problematic when used to analyse a mixture, especially when concerning classical drugs which are often adulterated by 'cutting' (Preble and Casey, 1972). This is where the pure form is adulterated with cheaper bulking agents; this could happen at each stage of the distribution process. Moreover, with NPS, the producer would press the substance into a pallet, pill or tablet (Vice, 2017).

This means there are fewer bulking agents as it is not broken down and bulked at each stage of distribution, therefore less likely to mask any spectra.
With the use of Raman to analyse the contents of samples, it gave useful primary information about what was being taken at Glastonbury in 2011. It should however be noted that this is a

small representation of what was being taken, this being two-fold. Firstly, not all samples are Raman active or able to be scanned by the Raman Analyser.

Those substances which are blotted onto paper cannot be analysed, as the laser is too powerful and will char the paper.

In the sample boxes were mushrooms, which species origin still remains unknown however they could not be scanned as organic material will char, as again the laser is too powerful. Whilst mushrooms would need to be analysed via different means as most instrumental techniques would struggle, the point remains for a substance like black-tar heroin, or such the like that Raman would be unable to analyse these types of samples. This is complementary to the guidelines given by the UN in the document titled, "Guidelines on Raman Handheld Field Identification Devices for Seized Material"

Secondly, these samples are only what people have discarded. Whilst it is hoped that the samples taken and scanned are representative of what was being used en masse, it has also shown that there was not a high amount of NPS use during a time when a high usage was supposed. This is why it has been vital during this research to use secondary sources, to gain a proper sight of what was happening during at that time.

Whilst the use of secondary sources has been vital for contemporaneous commentary, the use of secondary sources of information comes with some issues. Secondary sources of information especially from the mass media may not be accurate. When regarding the mass media, freedom of the press allows the author to express their opinions without interference (UN General Assembly, 1948). This means that secondary sources of information can be presented as fact but maybe somebody's opinion. Also, some sources for the mass media are anecdotal, i.e. a personal account from a member of the public; which will be biased, so whilst anecdotal evidence can be incredibly informative it should be used with caution.

Secondly, 'Publish or Perish' is a term used in academia to describe the need to continue research and publishing to continue on a career path (Doyle et al., 2012). This has led to research that may have been rushed and is not entirely reliable, because of this the secondary sources need to be reviewed before inclusion.

The reviewing process is to find many sources that corroborate the same idea, should many sources present the same results then there is a higher chance of them being good sources. Should there be a single source of information, presenting its own evidence with little-to-no other sources then it should be excluded. However, on the whole most of the sources used for this have been concurrent with one another, but it is still a risk that needs to be identified whilst working for optimum results.

Conclusion

Taking all of this into consideration, the trends around NPS have been assessed. It can be concluded that there was indeed a mass influx of these substances being imported and used in the UK. The government set out in 2013 to fully assess the best way to deal with this problem that was arising. This culminated in the Psychoactive Substance Act 2016, with the view to protect the general public by restricting access to these substances. The statistics shows that the Act was successful as head shops are now closed and the statistics are showing a reduction in deaths related with NPS. The Psychoactive Substances Act 2016 differed from that of the Misuse of Drugs Act 1971 by the fact there is no crime for possession - except in a custodial setting, of a psychoactive substance under the Psychoactive Substances Act 2016. This shows that the law aimed to directly limit the sale and production of NPS to reduce harm to the general public. Whilst it may not have acted as a deterrent to habitual users, it has stopped the average member of the public from gaining access to such substances. On the whole the Act has been successful in its aims in reducing the harm and protecting the public.

Further work could be taken in conjunction with this work. During this Raman was used in the rapid-scanning of samples, although due to constraints it wasn't possible to confirm the identification of substances with the use of control samples. In further work, these would be scanned, alongside common cutting agents.

With additional scanning, it could be possible to fully assess how additives can affect the Raman spectrum. Gas Chromatography-Mass Spectrometry could also be utilised to assess how accurate the identification via Raman is. This would be helpful as chromatography will separate out each component, which could greater inform the spectroscopy. Overall, this research project has shown positive aspects into the use Raman spectroscopy in rapid-scanning of NPS, which can be expanded on with complementary research as discussed.

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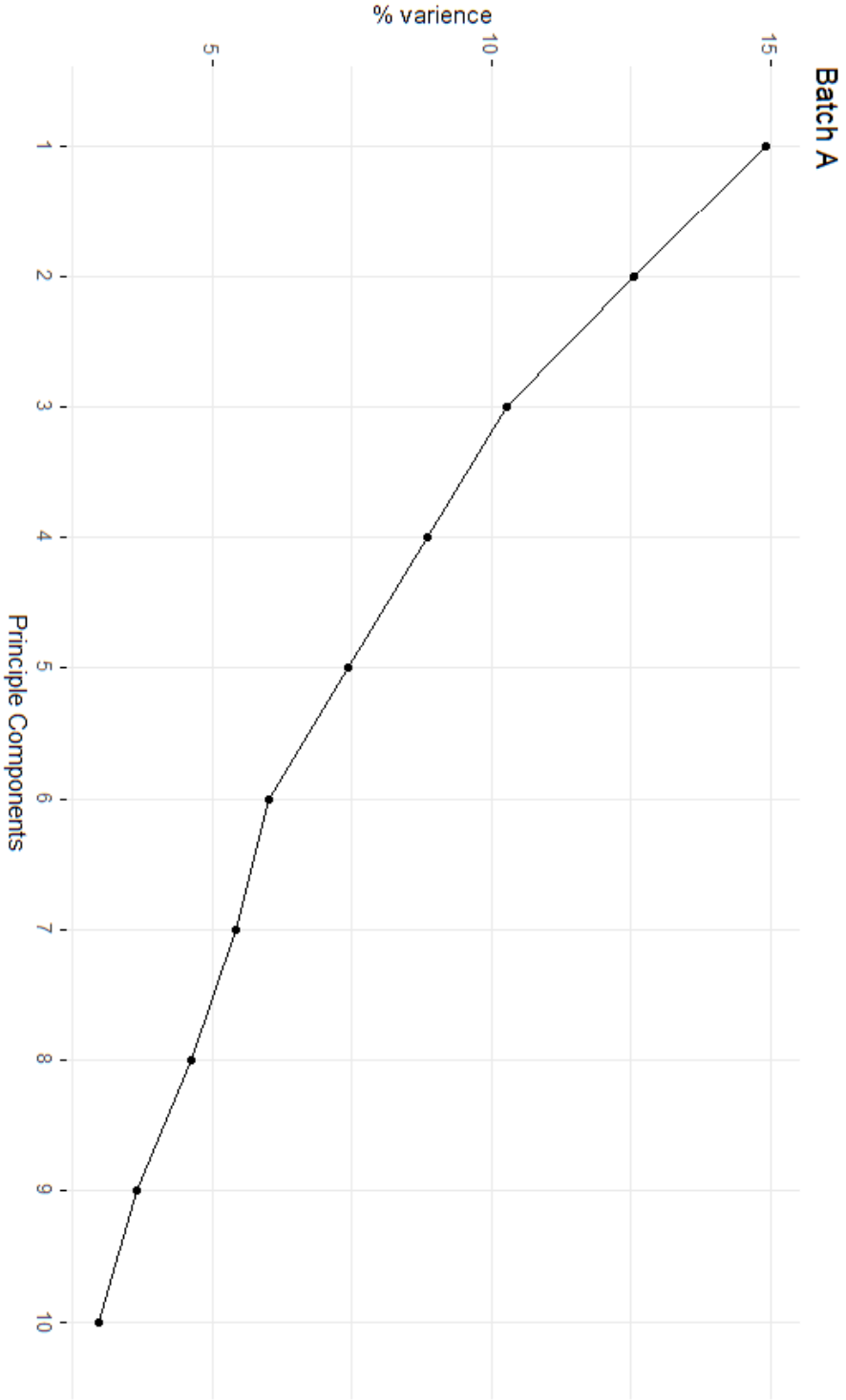
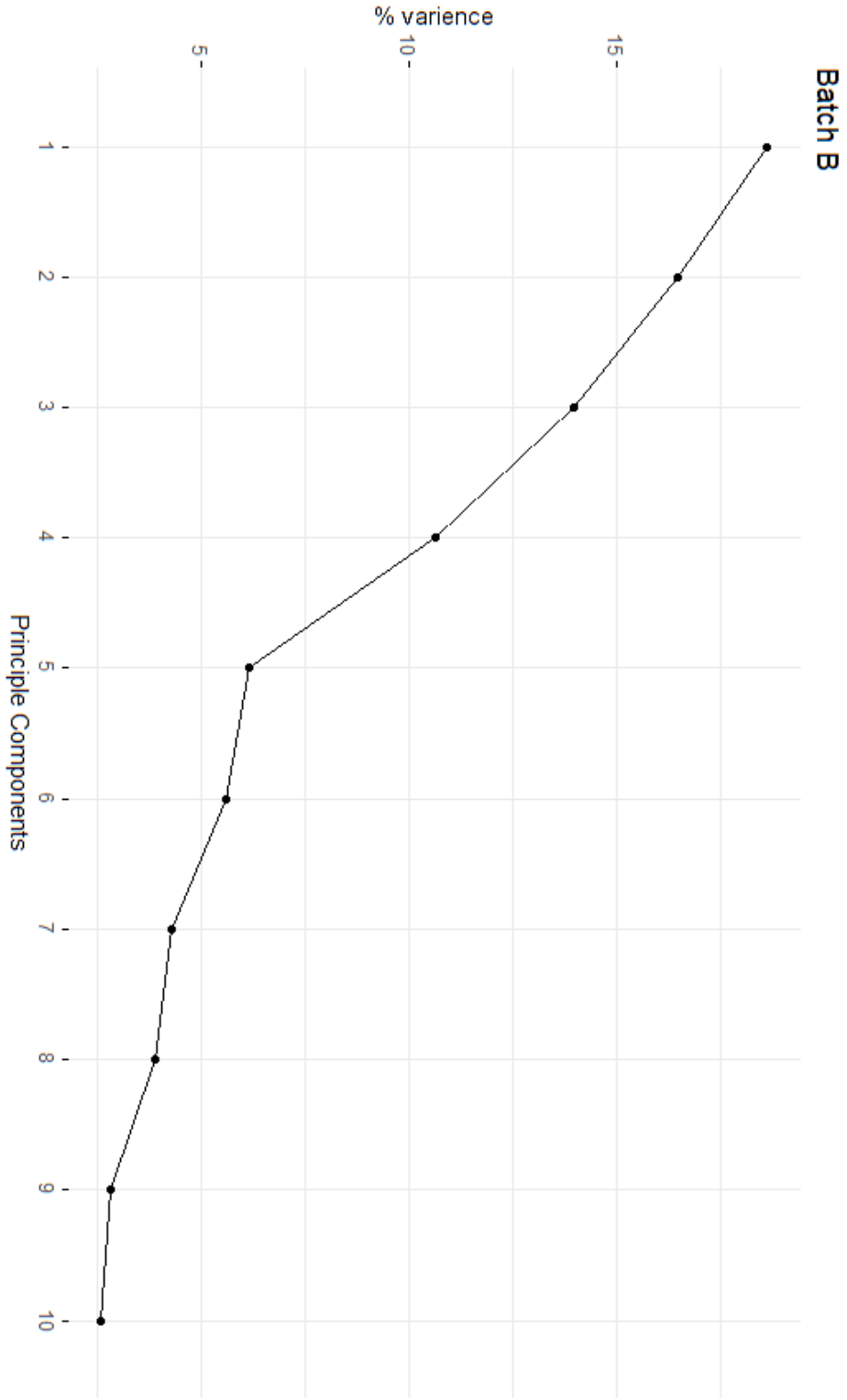
Appendix A – All scree plots

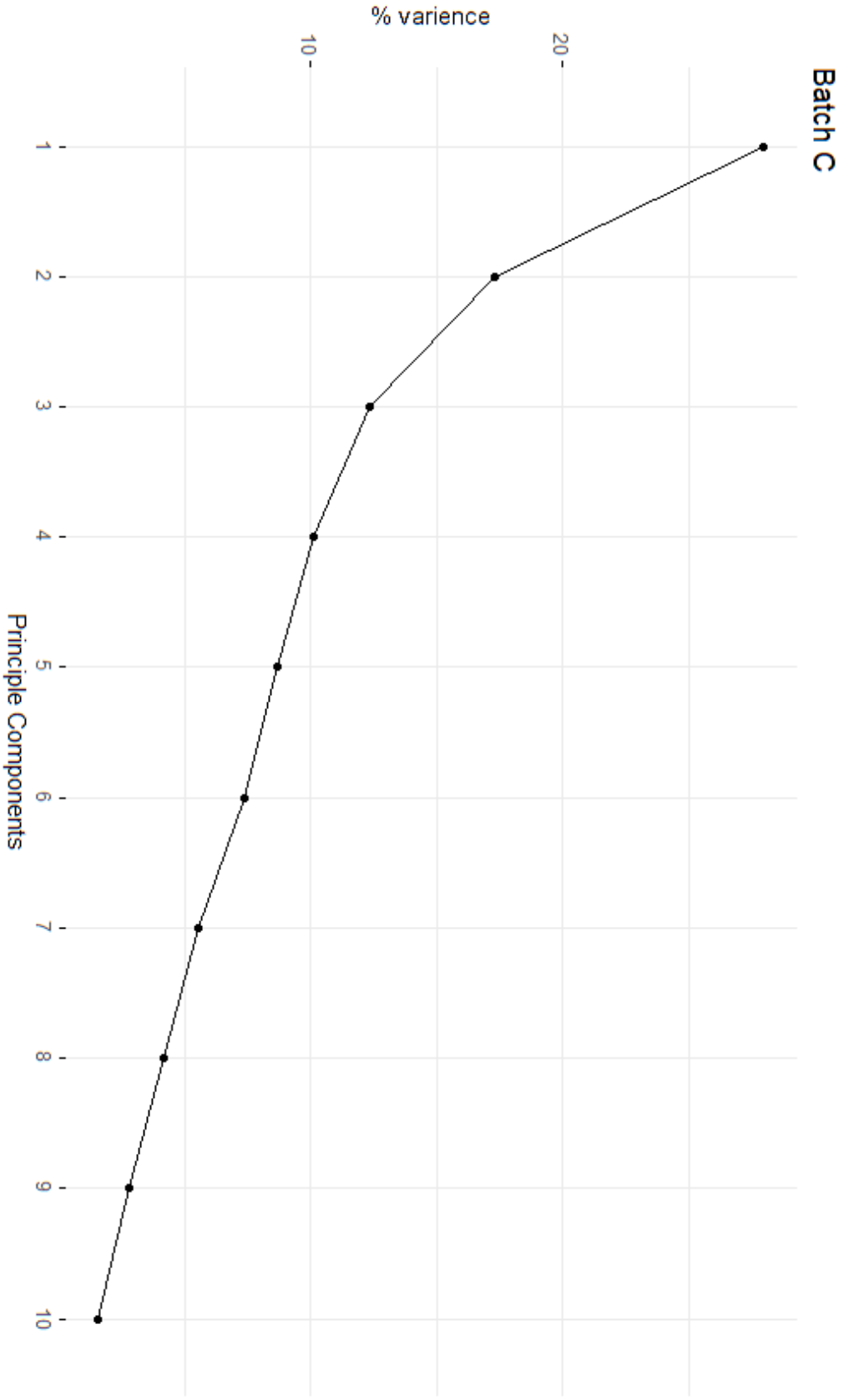
A1 – Scree plot for Batch A of substances scanned taken from the amnesty bins at the Glastonbury Festival 2011.



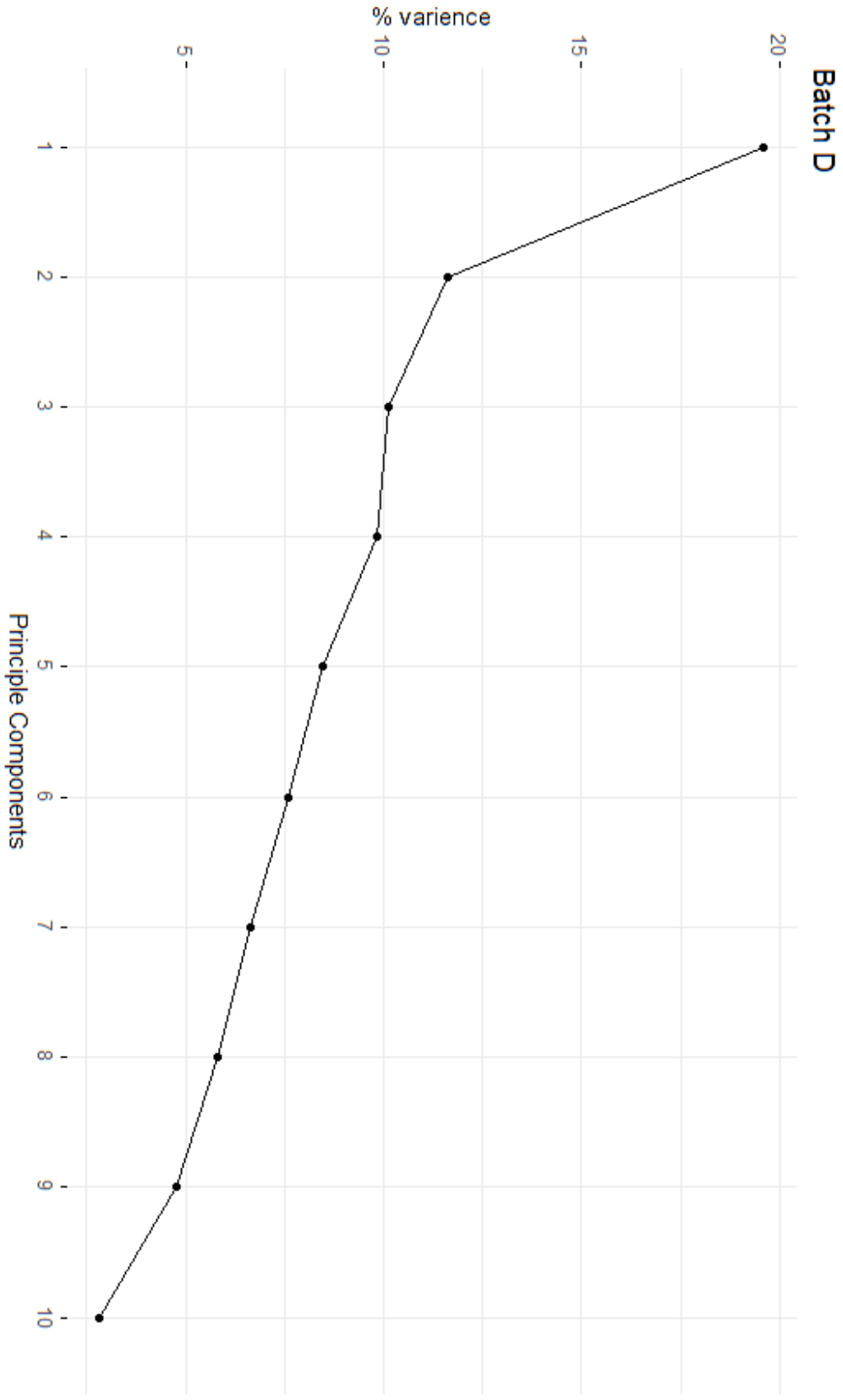
A2 - Scree plot for Batch B of substances scanned taken from the amnesty bins at the Glastonbury Festival 2011.



A3 - Scree plot for Batch C of substances scanned taken from the amnesty bins at the Glastonbury Festival 2011.



A4 - Scree plot for Batch D of substances scanned taken from the amnesty bins at the Glastonbury Festival 2011.



A5 - Scree plot for all batches of substances scanned taken from the amnesty bins at the Glastonbury Festival 2011.