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Comparison of Smoke Yield Data Collected from Different Laboratories*

by Beatrice Teillet [1], Xavier Cahours [1], Thomas Verron [1], Stéphane Colard [2], and Stephen W. Purkis [2]

[1] *SEITA, Imperial Tobacco Group, 48 rue Danton, 45404 Fleury-les-Aubrais, France*
[2] *Imperial Tobacco Limited, P.O. Box 525, Winterstoke Road, Bristol BS99 1LQ, UK*

SUMMARY

In the context of increasing tobacco product regulations, more requirements are observed for the reporting of smoke constituent yield data and its variability e.g., US Food and Drug Administration (FDA). The objective of this work was to evaluate the relevance of the short term standard deviation to describe the variability of measurements using the dataset of the CORESTA 2006 Joint Experiment which included a number of cigarette smoke constituents more recently identified by FDA for reporting. Their testing protocol required the analysis of Kentucky Reference cigarettes 2R4F and 1R5F performing five replicates run over consecutive days, repeated during three different time periods. This dataset provided access to different sources of smoke yield variability across measurements: short term and medium term within-laboratory variability and among-laboratory variability. For each reference cigarette, analysis of variance on one factor (laboratory) combined with the Newman-Keuls multiple range test was performed to compare data generated across laboratories. Results showed that the expression of yield variability as an individual standard deviation (describing repeatability) gives erroneous conclusions due to the major contribution of among-laboratory variability not being taken into account. The different sources of variability can be taken into account in the comparison using the critical difference, as described in the ISO Standard 5725 part 6. This paper shows the importance of having i) the appropriate statistical methods to compare results from different laboratories in order to avoid erroneous conclusions, and ii) validated and standardized methods with known precision across laboratories. Moreover, it was demonstrated that the number of replicates had only a minor effect on product comparison on the basis of the critical difference as a function of repeatability and reproducibility of the methods. [Beitr. Tabakforsch. Int. 25 (2013) 662–670]

ZUSAMMENFASSUNG

Vor dem Hintergrund zunehmender Regulierungen für Tabakerzeugnisse werden höhere Anforderungen an die Meldung von Daten zu Ausbeuten von Rauchbestandteilen und ihrer Variabilität beobachtet (z.B. FDA). Ziel dieser Arbeit war die Bewertung der Relevanz der kurzfristigen Standardabweichung zur Beschreibung der Variabilität von Messungen unter Verwendung des Datensatzes des CORESTA 2006 Joint Experiments, welcher eine Reihe von Bestandteilen von Zigarettenrauch umfasste, die nunmehr an die FDA gemeldet werden müssen. Deren Prüfplan sah die Analyse der Kentucky-Referenzzigaretten 2R4F und 1R5F vor, wobei fünf Bestimmungen an aufeinander folgenden Tagen durchgeführt und in drei verschiedenen Zeiträumen wiederholt wurden.
Mit diesem Datensatz wurde der Zugang zu verschiedenen Quellen von Variabilität der Rauchausbeuten über die Messungen hinweg ermöglicht: kurz- und mittelfristige Variabilität innerhalb von Laboren und zwischen Laboren. Für jede Referenzzigarette wurde eine einfaktorielle (Labor) Varianzanalyse in Kombination mit dem Newman-Keuls-Multiple-Range-Test durchgeführt, um die in den einzelnen Laboren generierten Daten zu vergleichen. Die Ergebnisse zeigten, dass die Variabilität der Ausbeuten als individuelle Standardabweichung (die die Wiederholgenauigkeit beschreibt) zu falschen Schlussfolgerungen führt, da die große Rolle der Variabilität zwischen den Laboren dabei nicht berücksichtigt wird. Die unterschiedlichen Quellen der Variabilität können in einem Vergleich mittels der kritischen Differenz, entsprechend der Beschreibung in der ISO-Norm 5725 Teil 6, berücksichtigt werden. In unserer Arbeit wird die Bedeutung i) geeigneter statistischer Methoden beim Vergleich der Ergebnisse verschiedener Labore zur Vermeidung falscher Schlussfolgerungen sowie ii) validierter und standardisierter Methoden mit bekannter Genauigkeit bei allen Laboren aufgezeigt. Darüber hinaus

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wurde nachgewiesen, dass die Anzahl der Wiederholungsbestimmungen nur eine geringe Auswirkung auf den Produktvergleich auf Grundlage der kritischen Differenz als Funktion der Wiederholgenauigkeit und Reproduzierbarkeit der Methoden hatte. [Beitr. Tabakforsch. Int. 25 (2013) 662–670]

RESUME

Dans un contexte réglementaire en perpétuelle évolution, nous faisons face à une augmentation du nombre de données à déclarer : moyennes et écart-types des mesures des taux des composés de la fumée (e.g. FDA). L'objectif de ce travail a été d'évaluer la pertinence de reporter l'écart-type pour décrire la variabilité des mesures en utilisant les données générées lors de l'analyse inter-laboratoire CORESTA 2006. Ce jeu de données a l'avantage de contenir des taux de composés de la fumée récemment citées par la FDA pour déclaration. Le protocole de test stipulait d'analyser des cigarettes de référence Kentucky 2R4F et 1R5F en effectuant pour chaque composé de la fumée cinq répétitions par jours sur trois périodes différentes.
Ce jeu de données permet de prendre en compte les différentes sources de variabilité qui peuvent affecter les mesures des composés de la fumée: variabilité intra-laboratoire et inter-laboratoires. Pour chaque cigarette de référence, l'analyse de variance à un facteur (laboratoire) combinée avec le test multiple de Newman-Keuls a été effectuée afin de comparer les données obtenues par les différents laboratoires. Les résultats montrent que l'expression de la variabilité des rendements en utilisant l'écart-type individuel (décrit comme la répétabilité) donne des conclusions erronées en raison de l'importante contribution de la variabilité inter-laboratoires qui n'est pas prise en compte. Les différentes sources de variabilité peuvent être prise en compte dans la comparaison en utilisant la différence critique, comme décrit dans la norme ISO 5725 (partie 6). Cette publication montre l'importance d'avoir i) des méthodes statistiques appropriées pour comparer des résultats provenant de différents laboratoires et ii) des méthodes validées et standardisées afin de connaitre leurs précisions. En outre, nous avons démontré que le nombre de répétitions n'a qu'un effet mineur sur la comparaison de produits lorsqu'elle utilise la différence critique calculée à partir de la répétabilité et de la reproductibilité des méthodes. [Beitr. Tabakforsch. Int. 25 (2013) 662–670]

1. INTRODUCTION

The number of initiatives to regulate cigarette smoke constituents beyond "tar", nicotine and carbon monoxide is increasing (1–6). The objective of existing and proposed regulation is presumably either to gain a better understanding of the products; to be able to discriminate between them or to impose limits on selected constituents. On a global scale, the WORLD HEALTH ORGANIZATION (WHO), through its study group on Tobacco Product Regulation (TobReg) published a strategy for tobacco regulation based on product assessments, with the goal of reducing the mainstream smoke levels of selected constituents (7). TobReg proposed a list of constituents selected on the basis of an assessment considering i) toxicity data from animals and humans, ii) variation in constituent levels across brands, iii) the potential for the constituents to be lowered, and iv) the inclusion of smoke constituents from different chemical classes in both particulate matter and vapour phase. These smoke constituents were divided into two sub-sets of nine constituents. Maximum smoke emissions normalized to nicotine would be mandated for constituents in the first subset whereas those in the second subset would require yield-reporting. Recently, the US FOOD AND DRUG ADMINISTRATION (FDA) has published, under the Tobacco Control Act, a list of "harmful and potentially harmful constituents" which must be tested and reported by cigarette manufacturers (6). However, standardized methods, which would meet the requirements of an international standard do not exist for any of these constituents, apart from ISO 22634 related to the determination of benzo[*a*]pyrene in mainstream smoke (8). Collecting such smoke yield data may provide useful information on commercial cigarettes although any comparison between products must take into account all the sources of variability likely to affect the measurements, in order to avoid misleading conclusions. Examples of potential data misinterpretation due to temporal variability within one laboratory (9) and among laboratories (10) have been discussed previously. PURKIS et *al.* have recently reviewed the current activities on smoke constituent measurements including yield variability and highlighted the factors influencing the variability of results (11). It was concluded that if smoke constituents regulation were to be implemented, a standardized and a science-based approach would be the pre-requisite for the generation and comparison of data.
Even so, some regulators require manufacturers to provide smoke yields on their products using non-standardized methods. In some cases, it is recommended or required to provide the mean and the standard deviation with the corresponding number of replicates in order to report variability (6). However, such information obtained within one laboratory can be misleading if it is used to compare data obtained in different laboratories (12, 13). This paper provides examples of the consequences of using standard deviation to express variability regardless of the number of replicates.
The comparison of smoke yields obtained in different laboratories is relevant only if all the sources of variability are taken into account. Consequently, the use of the repeatability and reproducibility, defined as the precision of the method, is the most suitable approach to take into account the full variability into the comparison (12). Based on the limits of the repeatability and reproducibility of the method, ISO 5725 part 6 describes and recommends the use of the critical difference (CD) (14) which has been used for the comparison of cigarette smoke yields in this paper.

2. EXPERIMENTAL

The first part of this paper reviews the dataset from the CORESTA 2006 Joint Experiment (15) which was performed in order to assess the different methods applied

among different laboratories. Nineteen laboratories participated and each laboratory applied its usual methods for the determination of smoke constituent yields. The testing protocol required the analysis of the Kentucky 2R4F and 1R5F Reference cigarettes performing five replicates completed over one or two consecutive days in each of three independent experiments with a minimum of one week between each experiment. A total of 15 results were provided by each laboratory on each reference cigarette and each smoke component. The equivalence of the data generated across laboratories has been investigated using statistical methods based on the studies of variance as an expression of the standard deviation. First, the analysis of variance (ANOVA) for each reference cigarette with the laboratory as a factor was performed on the full dataset, including all 15 replicates. Then, a complementary method, the multiple range comparison test described by NEWMAN-KEULS (16, 17) was applied to demonstrate the potential differences across the laboratories. Finally, an evaluation of the contribution of laboratory, time and replicates to the total variability, was performed on the full dataset using hierarchical ANOVA.

In the second part of this paper, comparisons of cigarettes analysed in different laboratories were carried out using the CD. For illustrative purposes, comparisons were carried out using commercial cigarettes analysed in two different laboratories. Cigarette specifications are given in Table 1.

Table 1. Cigarette specifications

Product description		Brand 1	Brand 2
Blend		US blend	US blend
Geometry	Tobacco Rod lenght (mm)	62	56
	Filter length (mm)	21	27
Filter type		CA	CA
Filter ventilation (%)		19	31
NFDPM (mg) under ISO regime		10.2	7.5
Nicotine (mg) under ISO regime		0.81	0.60
CO (mg) under ISO regime		10.3	8.4
Puff number under ISO regime		6.8	6.2

As the analyses were carried out in different laboratories the comparisons must be based on the reproducibility of the methods. Therefore, only figures resulting from recommended or standardized methods can be compared. Table 2 lists the twenty one smoke constituents for which the laboratories applied the existing recommended or standardized methods.

The CD is the smallest difference between two results so that they can be considered as statistically different taking into account all factors contributing to the variability of results. If the results come from two different laboratories (A and B), the critical difference is calculated from the equation [1]:

$$CD = \sqrt{R^2 - r^2\left(1 - \frac{1}{2n_A} - \frac{1}{2n_B}\right)} \qquad [1]$$

Where

CD = Critical Difference at the 95% probability level

n_A = number of analyses performed by the laboratory A

n_B = number of analyses performed by the laboratory B

R = Limit of reproducibility of the method

r = Limit of repeatability of the method

Table 2. Methods for smoke analysis under the ISO smoking regime

Smoke constituent	Method	Reference
Acetaldehyde	CRM 74	(20)
Acetone	CRM 74	(20)
Acrolein	CRM 74	(20)
Acrylonitrile	CRM 70	(21)
Benzene	CRM 70	(21)
Benzo[*a*]pyrene	CRM 58	(22)
Butyraldehyde	CRM 74	(20)
1,3-Butadiene	CRM 70	()21
Carbon monoxide	ISO 8454	(23)
Crotonaldehyde	CRM 74	(20)
Formaldehyde	CRM 74	(20)
Isoprene	CRM 70	(21)
MethylEthyl ketone	CRM 74	(20)
NFDPM ("tar")	ISO 4387	(24)
Nicotine	ISO 10315	(25)
NAB	CRM 75	(19)
NAT	CRM 75	(19)
NNK	CRM 75	(19)
NNN	CRM 75	(19)
Propionaldehyde	CRM 74	(20)
Toluene	CRM 70	(21)

To determine whether or not data originating from two laboratories is statistically different, the absolute difference between the two results is compared to the CD. If the difference is less than the CD, there is no statistically significant difference between the two laboratories. By contrast, if the difference is greater than the CD then there is a statistically significant statistical difference. In order to represent all the yield comparisons on a single graph, the difference between yields from laboratories A and B and the CD for each smoke compound have been normalized to the mean of yields from A and B, and expressed as a percentage.

3. RESULT AND DISCUSSION

3.1 Product comparison based on laboratory variability

Some regulators require manufacturers to report a list of smoke constituent yields on their products. In some cases, they recommend that the standard deviation with the corresponding number of replicates is reported to provide information on variability. Most of these yields are derived from methods which had not gone through any formal standardization process and for which neither levels of within- nor among-laboratory variability were determined. These yields collected from different laboratories, whilst

informative, should not be compared on the basis of the standard deviation reported by each laboratory.

The standard deviation obtained during analysis only reflects the variability in one laboratory at a certain period of time and does not take into consideration the method and among-laboratory differences. We carried out a comparison of the results given by each laboratory during the CORESTA 2006 Joint Experiment using statistical methods based on a standard deviation including analysis of variance (ANOVA) and a multiple range comparison test. Of the 16 smoke constituents investigated, ANOVA results gave statistically significant differences (p-value < 0.0001) between laboratories for the two reference cigarettes (1R5F and 2R4F) for all constituents.

Additionally, the multiple range test (i.e. Newman-Keuls) was performed to classify individual laboratory means. If the standard deviations estimated in the laboratories were representative of the variability affecting the measurements of the same product (e.g., 2R4F or 1R5F) then mean results from all the laboratories should belong to the same group. However, if the means were significantly different, based on standard deviation, then several groups will be generated according to the scatter of the means. Figure 1 represents the number of statistically different groups (Newman-Keuls test with a 95% level of confidence) observed for several smoke constituent yields from the same product (2R4F or 1R5F) analysed in different laboratories. Depending on the smoke compounds, the observed number of different groups ranges from 4 to 11 for the 2R4F and from 5 to 8 for the 1R5F. In other words, when using within-laboratory standard deviation to differentiate between products, the same product measured in different laboratories might be considered as statistically different products due to the among-laboratory variability.

In order to investigate the contribution of among-laboratory and within-laboratory variability, including time and replicates to the total variability, a hierarchical ANOVA was performed on the CORESTA 2006 Joint Experiment dataset. Figures 2 and 3 summarize the relative distribution of the variability for each smoke constituent yield obtained with reference cigarettes 2R4F and 1R5F, respectively. The results show that the variability is associated with:

- Replicates (within-laboratory standard deviation of the mean in a short time period) represent a minor part of the total variability from 5% to 25%.
- In some cases the time variability (within-laboratory standard deviation of the mean in a long time period) can be very low (1%) or in other cases can contribute as much as the variability of replicates (25%).
- Among-laboratory variability is the major source of variability ranging from 62% to 93%.

Consequently, a comparison of results from different laboratories based on within-lab standard deviation can generate erroneous conclusions if among-laboratory is important relative to within-laboratory variability. For smoke constituent analysis, the among-laboratory component represents the major source of variability (15, 18).

3.2 Product comparison based on the critical difference

In order to allow comparisons between two cigarette smoke yields obtained in two different laboratories, the difference between these two yields must be compared with the CD. The CD takes into consideration each of these 3 components of variability:

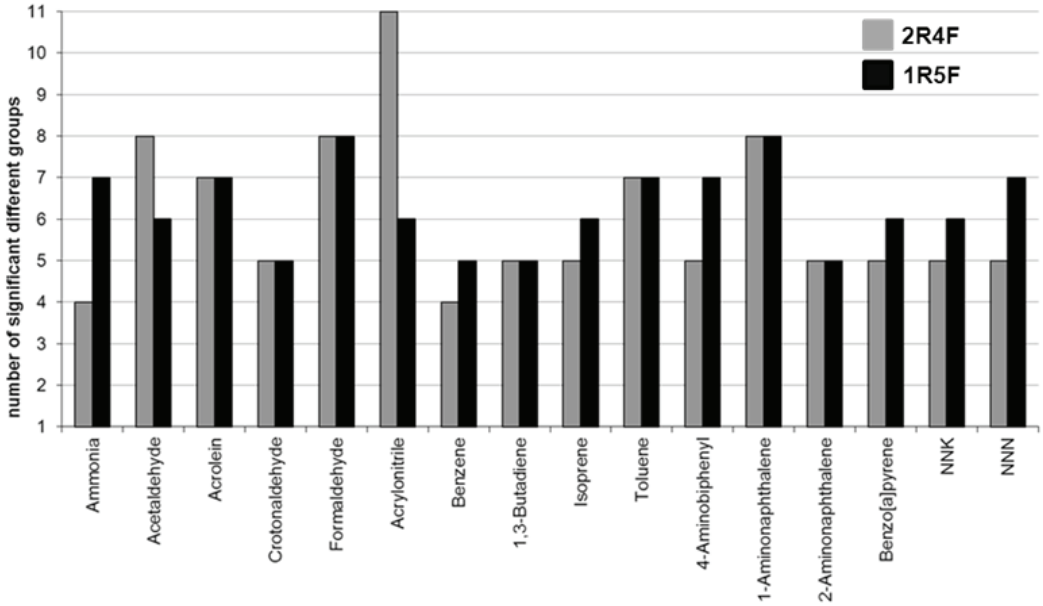

Figure 1. Number of statistically different groups (Newman-Keuls test at 95%) observed for several smoke constituent yields for the same product (Kentucky Reference 2R4F or 1R5F cigarettes) analysed in different laboratories in the CORESTA 2006 Joint Experiment.

- Repeatability - an expression of the precision under conditions where the results of independent assays are obtained by the same analytical procedure on identical samples in the same laboratory, by the same operator, using the same equipment and during a short interval of time;
- Intermediate precision - an expression of the precision under conditions where the results of independent assays are obtained by the same analytical procedure on identical samples in the same laboratory, with different operators and using different equipment and during a given time interval;
- Reproducibility - an expression of the precision under conditions where the results are obtained by the same analytical procedure on identical samples in different laboratories, with different operators and using different equipment.

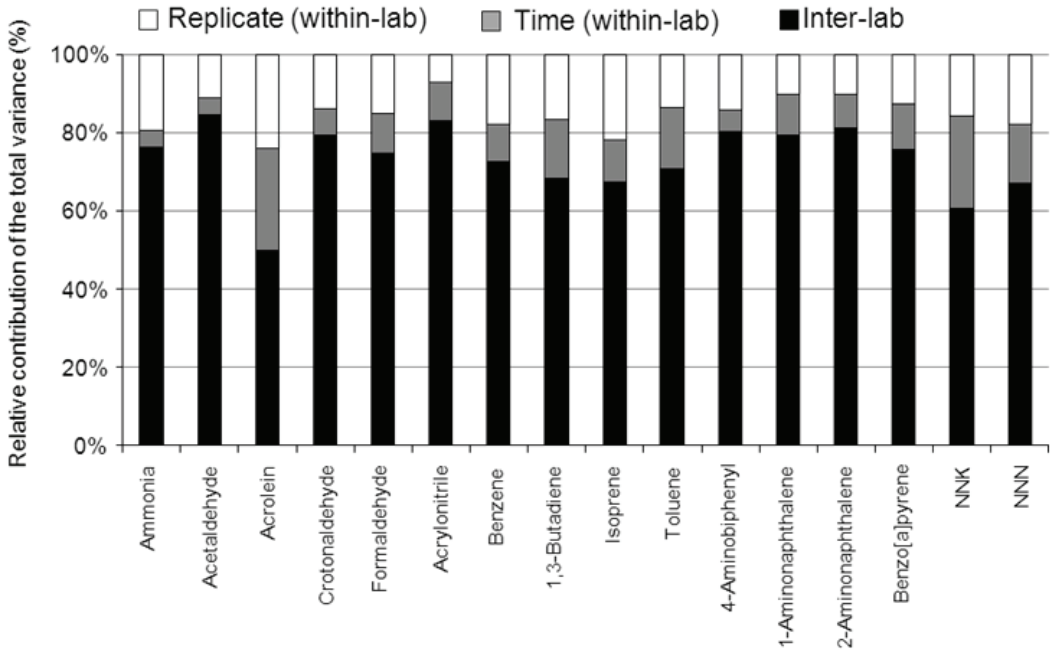

Figure 2. Contribution of among- and within-laboratory variability (time and replicates) to the total variability in the CORESTA 2006 Joint Experiment for the Kentucky Reference cigarette, 2R4F.

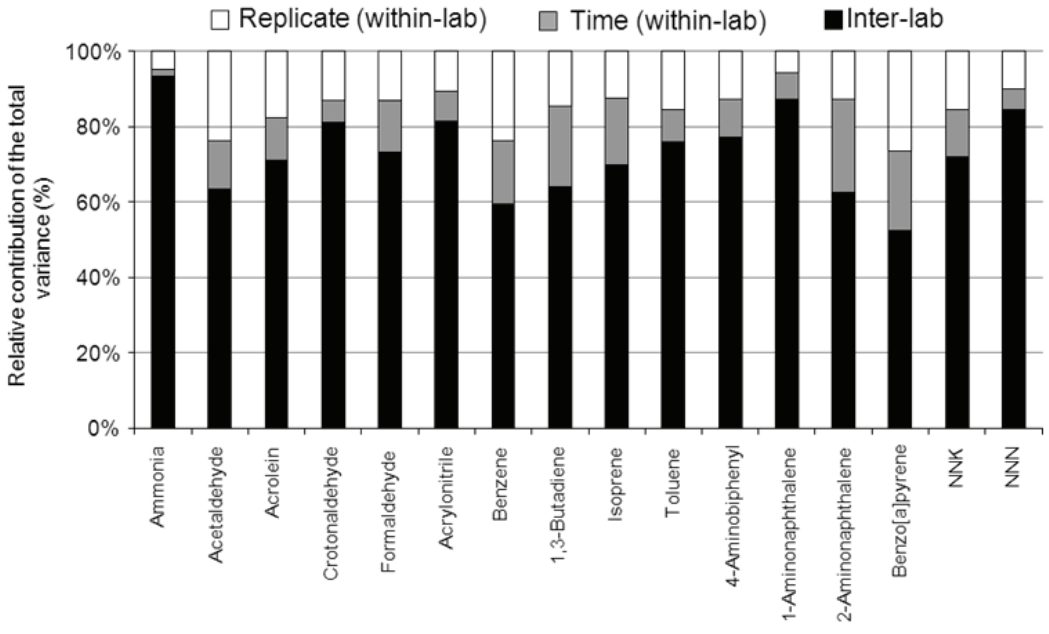

Figure 3. Contribution of among- and within-laboratory variability (time and replicates) to the total variability in the CORESTA 2006 Joint Experiment for the Kentucky Reference cigarette, 1R5F.

Figure 4 shows the comparison of twenty-one smoke constituent yields from the same commercial cigarette brand (Brand 1) obtained in two different laboratories.
Figure 5, on the other hand, shows a comparison of two different commercial cigarette brands (Brand 1 and Brand 2).
In Figures 4 and 5, the white and black bars correspond to the normalized differences in smoke constituent yields between the two cigarettes. The direction indicates the sign of the difference: The bars on the left side indicate lower yields from laboratory B than from laboratory A, and the bars on the right side indicate higher yields from laboratory B than from laboratory A. The grey bars represent the normalized CD based on repeatability and reproducibility of each method. In other words, it represents the ability to discriminate two products. If the difference is lower (white bars) than the CD of the method, there is no statistically significant difference in the constituent yield between the two cigarettes. By contrast, if the difference is higher (black bars) than the CD then there is a significant statistical difference in constituent yield between the two cigarettes.
The data indicates that smoke constituent yields of commercial cigarette (Brand 1) analysed in two different laboratories are not statistically significantly different (Figure 4). Even though the normalized difference is higher than 40% for certain smoke constituents (e.g., MethylEthyl ketone or formaldehyde), it cannot be concluded that there is a significant difference when taking the method variability into account.

Table 3. Impact oft the number of replicates on the critical differences of formaldehyde and NNN based on repeatability and reproducibility value of Kentucky Reference 3R4F cigarettes, as described in the CORESTA Recommended Methods 74 and 75.

Formaldehyde				
Mean yield (µg/cig)	Limit of repeatability (µg/cig)	Limit of reproducibility (µg/cig)	Number of replicates	Critical difference (µg/cig)
18.8	4.9	13.0	1	18.8
			3	18.4
			10	18.2
			20	18.2
NNN				
Mean yield (ng/cig)	Limit of repeatability (ng/cig)	Limit of reproducibility (ng/cig)	Number of replicates	Critical difference (ng/cig)
115.0	18.0	34.0	1	34.0
			3	30.7
			10	29.5
			20	29.1

However, two commercial cigarettes, showing different "tar" levels on the cigarette pack (Brand 1 and Brand 2) analysed in two different laboratories clearly show some significant differences in several smoke compounds yields: NNN, isoprene, benzene, methyl ethyl ketone, acetaldehyde, nicotine and "tar" (Figure 5). In general the product giving less "tar" yield (Brand 2) gives less smoke constituent yields.
According to equation [1], the options for decreasing the CD are to 1) decrease the method repeatability, 2) decrease the reproducibility, and/or 3) increase the number of replicates. Table 3 gives the impact of the number of replicates on the CD for NNN and acetaldehyde using the values of repeatability and reproducibility obtained with the reference cigarette 3R4F during the collaborative study for the development of CORESTA Recommended Methods 74 and 75 (19, 20). This estimation was performed by assuming that, as recommended in CORESTA methods, there is the same number of replicates ($n_A = n_B = n$) for analysing this reference cigarette in two laboratories, therefore the equation of the CD at 95% probability level is

$$CD = \sqrt{R^2 - r^2\left(\frac{n-1}{n}\right)} \qquad [2]$$

For one replicate, the critical difference is equal to the limit of reproducibility (R). An increase from three replicates to 20 replicates gives just a decrease of 3% and 5% of CD for formaldehyde and NNN, respectively. Therefore the CD is not substantially reduced by increasing the number of replicates. The repeatability of methods is linked to the methodology and can hardly be decreased without changing the method. The among-laboratory variability is the major source of variation and thus the best way to decrease the CD is to harmonize as much as possible the standard operational procedure between the laboratories in order to improve the reproducibility.

CONCLUSIONS

The current lack of standardized and validated methods for most cigarette smoke constituents results in the generation of data by various laboratories using different analytical methods. These data, whilst informative, cannot be compared on the basis of the standard deviation obtained during analysis only, because this standard deviation reflects the variability within a single laboratory, at a certain period of time and does not take into consideration the method and among-laboratory differences. An understanding of the method variability across laboratories is crucial for providing the informative context necessary to compare results produced over time in different laboratories. Therefore, any meaningful use of reported data will require the validation and standardisation of methods as a first step, as has been done for "tar", nicotine and carbon monoxide under the ISO smoking regime. Later after the determination of the method precision, described by repeatability and reproducibility, reported data can be compared taking into account all the variability to avoid erroneous conclusions. The method precision allows the determination of the critical difference, that is, the smallest difference between two results so that they can be considered as statistically different taking into account all the variability of results. The number of replicates has minimal effect on this comparison and regulatory requests for relatively large numbers of replicates are unnecessary and burdensome.

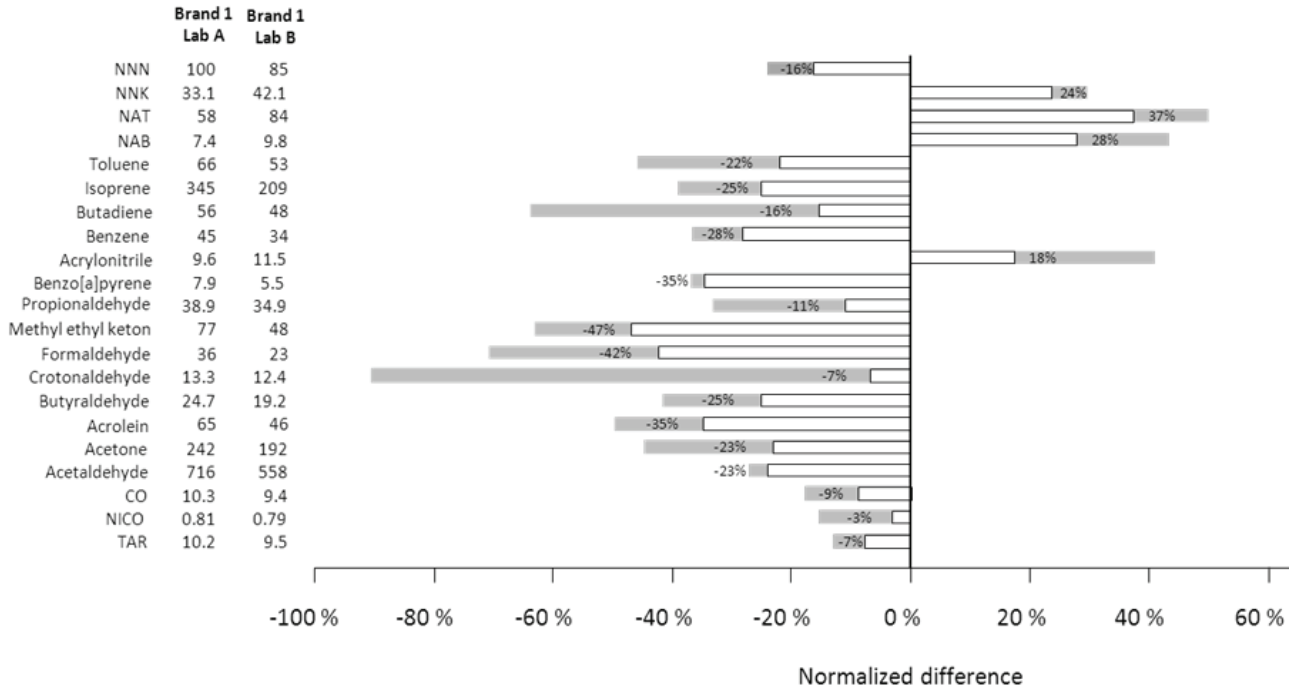

Figure 4. Comparison of smoke constituent yields for one brand of commercial cigarettes analysed in two different laboratories. White bars correspond to the normalized differences in smoke constituent yields between the two laboratories. Grey bars represent the normalized CD based on repeatability and reproducibility of each method. As the difference is lower than the CD of the method, there is no statistically significant difference in the constituent yield between the two laboratories.

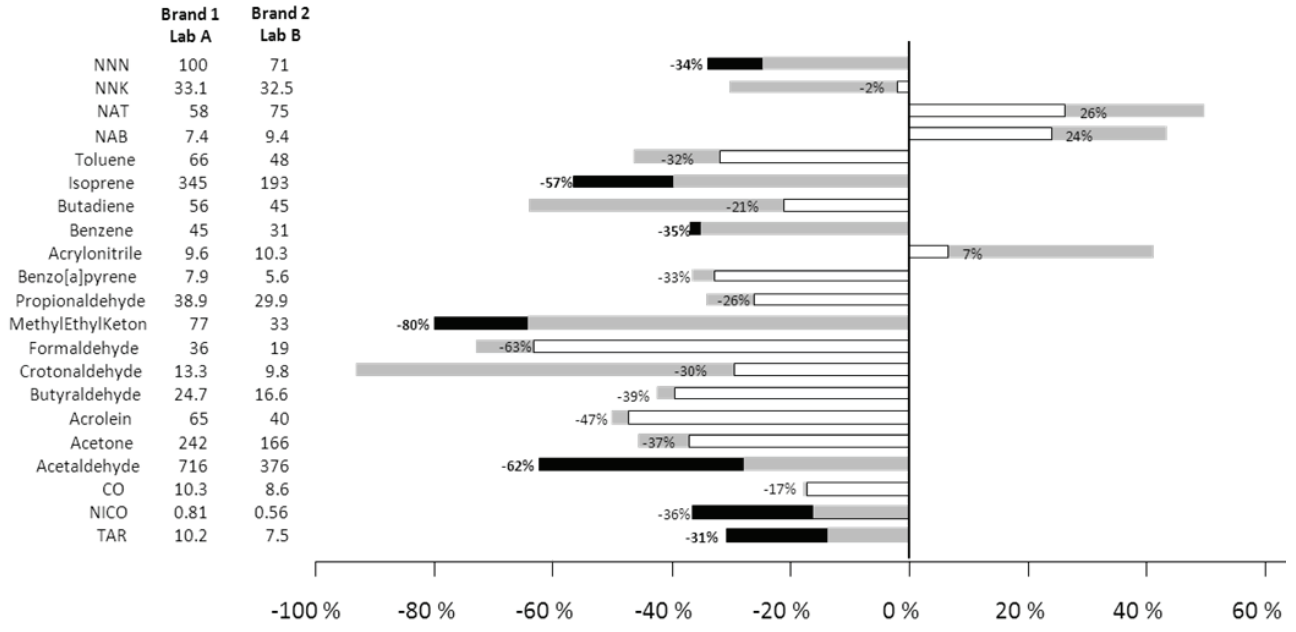

Figure 5. Comparison of smoke constituent yields from two different brands of commercial cigarettes analysed in two different laboratories. White and black bars correspond to the normalized differences in smoke constituent yields between the two cigarettes. Grey bars represent the normalized CD based on repeatability and reproducibility of each method. If the difference is lower (white bars) than the CD of the method, there is no statistically significant difference in the constituent yield between the two cigarettes. By contrast, if the difference is higher (black bars) than the CD then there is a significant statistical difference in constituent yield between the two cigarettes.

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Corresponding author:

Xavier Cahours
SEITA, Imperial Tobacco Group
48 rue Danton
45404 Fleury-les-Aubrais, France
E-mail: xavier.cahours@fr.imptob.com