Review Article

Optimizing Drug Distribution Logistics in the Community of Madrid

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Received: December 18, 2024; Accepted: January 06, 2025; Published: January 13, 2025

Abstract

Health-related services, and specifically drugs, are one of the most important economic activities in modern societies. Drugs, as a final medical product, constitute the basis for improving the quality of health services.

In this article, we propose as a general working hypothesis that better rationalization in the logistics distribution of drugs, through a combination of an optimal location of distribution centers, transport routes, and a rational selection of means of transport, could positively influence both the perceived quality of care and the quality of drugs by the user.

In addition, we study how to reduce energy consumption, the carbon footprint (CO_2), the risk of non-supply, refrigeration, and monitoring costs, and, ultimately, the final cost of centralized drug distribution.

On this basis, we have built a model taking all the data from the geographic locations of more than 2,500 pharmacies in the Community of Madrid, and with the help of the R program, the data have been classified into 'clusters' using minimum distances and giving different center solutions depending on the number of clusters.

Keywords: Medicines; Pharmacy; Pharmaceutical logistics; Community of Madrid; R logistics distribution; Carbon footprint; Green Logistics (GL)

The Current Situation of the harmaceutical Industry in Spain

Characterization of the Pharmaceutical Industry in Spain

In the last 25 years, the pharmaceutical industry in Spain has become a key sector of the Spanish economy, [1] of strategic nature as it is one of the drivers of Spanish exports, exporting pharmaceutical products, in 2022, for a value of more than 26,844 million euros [2] as a recipient of private investment in R&D and as a generator of quality employment.

The Spanish pharmaceutical industry is made up of 360 companies, and the turnover in pharmaceutical products in 2019, was 16,246 million euros [3].

In addition, the pharmaceutical industry indirectly generates, by knock-on effect, a significant associated economic activity, up to 76%, due to the degree of connection it has with other sectors of activity, such as health and retail trade, represented by a wide network of pharmacies throughout the territory through the different autonomous communities present in Spain [4].

That is, for every €100 of added value generated directly, the sector can create, together with other sectors, up to €76 more. It is responsible for 21% of all industrial R&D in Spain, produces more than €15 billion a year (24% of all high technology) and, in addition to the export of pharmaceutical products, is also one of the leaders in high technology exports, which account for 27% of the total in this chapter.

Therefore, in R&D, according to INE data, it concentrated 4.9% of total investment in 2020 (8.8% if public administrations and universities are excluded) and represents nearly 20% of investment in R&D in the manufacturing industry.

It employs more than 36,300 people and in terms of productivity, the performance of the pharmaceutical industry is particularly notable. The gross added value per employee is more than two times higher than the average value of the Spanish economy and the manufacturing industry.

The estimated value of investments during 2022 and 2023 will be around 1 billion euros per year, which represents a net asset renewal rate of around 27% per year [5].

Relationship between GDP and Pharmaceutical Expenditure in Spain

Pharmaceutical Expenditure in Spain by Autonomous Communities: Situation of the CAM in Relation to GDP

Pharmaceutical expenditures are one of the most important items in the health budget of autonomous communities [6,7].

For this reason, the government of Spain has decided to recover the sustainability mechanism for pharmaceutical expenditure, which links the growth of expenditure on medicines with that of GDP. This mechanism involved the return of more than \notin 450 million from the pharmaceutical industry to the State for excess expenditure (balance obtained only in the years 2018 and 2019) [8].

Citation: Hellin JE, Diaz REG. Optimizing Drug Distribution Logistics in the Community of Madrid. J Fam Med. 2025; 12(1): 1376.

Public health expenditures in 2021 in Spain, according to the report on Public Health EXPENDITURE STATISTICS 2021: The main results, of March 2023 [9], were \in 87,941 million, which represents approximately 7.3% of GDP. (Table 1, with a per capita expenditure of \notin 1,858. Spain's GDP in 2021 was \notin 1,222,290 million [10].

Regarding the classification of expenditures, the HR remuneration section is the most important (*Table No. 2, 44.1% in 2021*).

• Pharmaceutical expenditure is divided into 2 large blocks: hospital pharmaceutical expenditure and expenditure on pharmaceutical and health products by medical prescription or dispensing ordeThe first has experienced a strong increase due to the development of new drugs for cancer or hepatitis C.

• The second has grown less due to the rationalization and savings policies adopted by public administrations such as the prescription by active ingredient and the auction of generic drugs.

In this way, according to a functional classification of public health expenditure, the highest weight is associated with hospital and specialized services with €54,205 million, 61.6% of total consolidated expenditure in 2021. Pharmacy expenditure, expenditure derived from prescriptions, reimbursement of pharmaceutical expenses and expenditure on other products supplied directly to households would be in second place, Table no. 3, with €12,809 million or 14.6%, figure 1, of total consolidated expenditure, which amounted to €87,941 million in 2021.

 Table 1: Consolidated public health expenditure. Millions of euros, percentage of GDP and euros per inhabitant. Spain, 2017-2021.

	2017	2018	2019	2020	2021
Millions of euros	68.507	71.091	75.111	83.622	87.941
Percentage of GDP	5,9%	5,9%	6,0%	7,5%	7,3%
Euros per inhabitant	1.472	1.521	1.595	1.766	1.858

Table 2: Consolidated public health expenditure according to economic classification millions of euros. Spain, 2017-2021.

	2017	2018	2019	2020	2021
Workers' remuneration	30.212	31.312	33.608	36.457	38.778
Intermediate consumption	17.273	17.995	19.167	23.182	24.169
Fixed capital consumption	257	266	270	275	290
Agreements	7.674	7.915	8.099	8.383	9.010
Current transfers	11.944	12.252	12.602	12.957	13.657
Capital spending	1.147	1.350	1.365	2.368	2.038
Consolidated total	68.507	71.091	75.111	83.622	87.941



It is important to note that 7.9% of Spain's public health expenditures do not appear territorialized in the statistics. There is a slight correction in terms of consolidated public health expenditure in the sector, closing at &80,955 million, which represents 6.7% of GDP, with an average per capita expenditure of &1,716.

If we relate the expenditure and the population of each autonomous community, the highest health expenditure is in the Basque Country (€2,073/inhabitant), the Principality of Asturias (€1,965/h) and Navarra (€1,941/h).

The lowest expenditures are Andalusia (ϵ 1,486 / h), CAM (ϵ 1,536 / h) and Balearic Islands (ϵ 1,644/h).

However, it is much more complicated to find a relationship between pharmacy expenditure by autonomous community and GDP.

The GDP data for the CAM were estimated at \notin 234,639 million in 2021, with a growth of 5.4% (10), but we do not find pharmacy expenditure by territory. Only the total of \notin 12,809 million.

Being able to know the relationship between the GDP of each territory, and specifically in the case of the CAM, and pharmaceutical expenditure could constitute an objective indicator that would allow us to evaluate the efficiency and sustainability of health policies in pharmacy, as well as the potential economic and social impact of actions derived from a more efficient logistics distribution.

According to the data collected in the public expenditure budget (satellite accounts), the consolidated expenses in Pharmacy in the CAM are \notin 1,154,703,000 (Section 2.1 Non-market production) and as functional public health expenditure in pharmacy \notin 1,486,301,000 in 2021, see Table 3.4.13 in (11), (12) of which, through the official prescription of the National Health System, as of December 2021 it is \notin 1,396,239,159 with an increase of 7.05% compared to 2020 [13] and a national total, in 2021, of \notin 11,746,978,210 (Table 6).

According to the above data, total pharmaceutical expenditure (public and private) in CAM represented 1.57% of the CAM GDP in 2021, a figure lower than the national average (1.6%) and the European average (1.8%).

This suggests that CAM has a lower level of drug and medical product consumption per inhabitant than other Spanish and European regions.

Sale of Medicines in Pharmacies in Spain

Sales have increased significantly in the last 10 years. The net sales turnover in Spain in 2021 was approximately $\notin 10.77$ billion.

Table 3: Consolidated public health expenditure according functio	nal
classification. Millions of euros. Spain, 2017-2021.	

	2017	2018	2019	2020	2021
Hospital and specialty services	42.610	44.007	46.814	52.035	54.205
Primary health services	9.675	10.335	11.027	11.947	12.720
Public health services	769	782	823	1.788	2.560
Collective health services	1.840	1.855	1.973	2.063	2.195
Drugstore	11.223	11.506	11.789	12.121	12.809
Transfers, prosthetics & appliances	1.243	1.255	1.319	1.300	1.415
Capital spending	1.147	1.350	1.365	2.368	2.038
Consolidated total	68.507	71.091	75.111	83.622	87.941



Figure 2: Distribution of plants located in the CAM. Source: www.google. com/maps



	PHARMIACEUTICALEAFENSES TROUGH OFFICIAL FRESCRIPTION OF THE NATIONAL HEALTH STSTEM							
REGIONS	MONTHLY DATA			ACCUMULATED JANUARY-DECEMBER				
	2021	2020	%21/20	2021	2020	%21/20		
ANDALUCÍA	186.127.839	168.774.186	10,28	2.134.170.084	1.980.785.579	7,74		
ARAGÓN	31.094.586	29.201.011	6,48	356.007.807	339.953.711	4,72		
ASTURIAS	26.431.310	24.737.502	6,85	302.072.160	288.901.630	4,56		
BALEARES	21.621.474	20.518.723	5,37	248.439.353	234.954.100	5,74		
CANTABRIA	14.403.809	13.278.465	8,47	164.852.214	156.403.292	5,40		
CASTILLA LA MANCHA	48.784.863	46.058.588	5,92	568.420.111	542.348.519	4,81		
CASTILLA LEÓN	59.386.751	55.602.821	6,81	687.356.751	655.901.329	4,80		
CATALUÑA	143.935.389	133.801.594	7,57	1.623.421.499	1.527.998.723	6,24		
CANARIAS	51.077.829	48.090.104	6,21	592.464.615	556.812.214	6,40		
EXTREMADURA	30.227.453	28.083.101	7,64	352.267.875	332.510.541	5,94		
GALICIA	68.205.755	63.650.871	7,16	781.110.597	737.688.125	5,89		
MADRID	127.171.169	113.532.904	12,01	1.396.239.159	1.304.339.218	7,05		
MURCIA	37.179.950	33.761.804	10,12	422.116.791	392.394.675	7,57		
NAVARRA	12.916.507	11.984.826	7,77	147.436.383	138.089.759	6,77		
C. VALENCIANA	118.826.527	115.595.777	2,79	1.364.088.075	1.297.222.284	5,15		
PAÍS VASCO	44.373.789	42.241.428	5,05	496.490.429	486.654.928	2,02		
LA RIOJA	6.776.094	6.223.388	8,88	77.697.778	73.706.322	5,42		
CEUTA	1.475.843	1.381.530	6,83	17.030.384	15.981.377	6,56		
MELILLA	1.311.509	1.252.291	4,73	15.296.147	14.671.236	4,26		
NACIONAL	1.031.328.445	957.770.912	7,68	11.746.978.210	11.077.317.563	6,05		

The most sold medicines are those prescribed for conditions of the nervous system, which are 20% of the total, followed by those of the digestive, metabolic, and cardiovascular systems.

Distribution Sector Structure in Spain and the CAM

It should be mentioned that they will be classified as direct and indirect. In the direct sector we refer to production plants according to the manufacturing technology of the active ingredient and the use of the medicine (manufacture of active ingredients by chemical synthesis or by biological active ingredients). Regarding use, we segment for humans and for the veterinary field.

In the indirect sector, there are suppliers of materials to produce pharmaceutical products, those of Active Ingredients (APIs), those of packaging materials, and other consumables.

The four territories with the highest concentration are Catalonia, with 79 of the 173 plants, the CAM with 40 plants, Castilla y León with 14 plants and Castilla-La Mancha with 8 more plants. Together, they represent 82% of the production and 84% of the total direct human capital of the sector.

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We will only take into account those dedicated to the production of medicines in the commercial phase located in the CAM of the total number of establishments authorized by the AEMPS in the Spanish territory, as of March 2022, with more than 20 employees and classified according to their type of plant, Figure 2, namely: manufacturers of APIs, chemically synthesized medicines (human and veterinary use) and plants for medicines of biological origin. Location [15].

Systematic Review Process of Research Articles and Papers

To identify the different methods for establishing logistics routes and to structure the published knowledge on this topic, we have carried out a systematic review inspired by an adaptation of the procedures established by Alves and Mariano (2018).

The first step was to choose the available scientific databases or repositories in which to search for research papers and reference articles in the logistics distribution sector. Scopus and Web of Science (WoS) were chosen. Then, we identified the search terms to determine the keywords (for example: logistics methods drugstore, logistics processes in distribution of pharmaceutical products, logistics distribution from logistics centers to pharmacies, logistics distribution in pharmacies, evaluation of the best logistics route, binomial logistic regression vs. random forests, multinomial regression as a logistic method, etc.) and we selected papers in both Spanish and English.

The initial search process included 1,401 articles (from different selection processes and search criteria (2+150+129+20+1000). Then, the filtering process was carried out, eliminating 779 articles because they did not fit our purpose or because the logistic focus was only tangential (Figure 3). In the fourth stage, we worked with 64 articles that made up the preliminary sample to identify the logistic method used and the validation of its results. Finally, 32 are incorporated into the text as cited references.



Green Distribution and Logistics (GL): Methods to Establish and Measure Routes and Customer Preferences in Choosing a Pharmacy (others' lines of work)

In this way, we can identify different lines of work that range from the optimization of the logistics route in the distribution of drugs to the measurement and possible prediction of the choice of the pharmacy by its potential clients [5] when there is the possibility of evaluating the quality of the service [3], the price of the pharmaceutical specialty or the convenience of adopting "Green Logistics" (GL) practices not only as a formula to control climate change, but because they correlate positively with economic growth [7].

That is to say, that sustainable development depends, to a large extent, on the active application of GL practices is underlined by different authors [8,9] Evangelista, P., Santoro, L., & Thomas, A., 2018) in activities related to transport and storage in all commercial and industrial dimensions, which of course include those in the pharmaceutical field.

The growing demand for the application of GL practices and the search for criteria to optimize logistics supply routes for pharmacies have been determining factors for the construction of this article, in line with the work of other colleagues who have turned their attention to closer territories such as Italy, Germany, the United Kingdom [10-13] or further away such as Lithuania [16] Thailand [14] or China [15].

Regarding logistics route planning and optimization, we can say that very different methods are used, ranging from the first approach to the logistics problem called vehicle routing problem (VRP), the subsequent CVRP (Capacited Vehicle Routing Problem) [17] to **multinomial regression models with up to 8 significant variables** [2]. The objective was to "determine the main variables that influence consumer choice in the pharmaceutical sector, to generate a predictive model for competitive analysis."

Since Dantzigan and Ramser were the first to present the problem in 1959 and proposed the first formulation of mathematical programming with an algorithmic approach and years later Clarke and Wright, in 1964, formulated a heuristic that improved the previous approach, hundreds of models and algorithms have appeared for the optimal and approximate solution of the different versions of the VRP. There are applications for the solid waste, beverage, food, dairy, and newspaper industries [19-21].

In recent years, a significant number of improvements have been incorporated because of the use of more complex algorithms and the increase in the computing capacity of the computer equipment used [18].

In relation to multinomial logistic regression, or maximum conditional entropy model, multiclass logistic regression, "multinomial logit", polytomous logistic regression, or "softmax" regression, it is a statistical model that, given a set of independent variables, is used to predict the different possible results of a categorical distribution as a dependent variable. That is, when we have a categorical dependent variable with 2 or more unordered levels or discrete results, we use multinomial logistic regression [1]. We choose the most frequent or common category as the reference category, which will be one level of the dependent variable. The possibility or probability of being in any of the other categories is measured or compared with this reference category.

We call these relative probabilities logarithmic probabilities, and they will constitute the predictions of the logarithmic probability model.

Typically, this type of regression is performed with specific software that runs a series of individual binomial logistic regressions for M-1 categories. That is, for each of the categories except for the reference category.

There is different software on the market, such as, for example, SPSS annotated output, STATA annotated output or Project R. [21].

CO2 Emissions from Light Commercial Vehicles (LCVs)

LCVs account for more than 10 % of all road vehicles in the EU (EC Delft, 2017) and at least 9 % of greenhouse gas (GHG) emissions (DfT, 2017) because the number of kilometers traveled in this type of vehicle has been increasing throughout the Union (16) since 2009, probably due to a general increase in GDP.

Using R for Logistics Clustering

The packages used for this article are: cluster (Maechler et al. 2022), dbscan (Hahsler y Piekenbrock 2022), e1071 (Meyer et al. 2023), factoextra (Kassambara y Mundt 2020), fpc (Hennig 2023), GGally (Schloerke et al. 2021), kernlab (Karatzoglou, Smola y Hornik 2023), mclust (Fraley, Raftery y Scrucca 2022), mlbench (Leisch y Dimitriadou. 2021), scatterpie (Yu 2023), seriation (Hahsler, Buchta y Hornik 2023), tidyverse (Wickham 2023b) and the textbook (Tan, Steinbach y Kumar 2005): Chapter 7. Cluster analysis: basic concepts and algorithms.

Data Collection and Graphical Representation

The location data for the pharmacies have been obtained from the Community of Madrid and the National Geographic Institute of Spain to transform x and y into geographic coordinates. The data containing the 2,928 pharmacies in the Community of Madrid (CAM) are listed in x,y coordinates that will be used for the analysis we detail. To load the data, it was used: "read. csv2" y "file.choose". We name the file "farma" and mark the first rows with "head" (Figure 4).

We can see that there is a large concentration of data in the center of Madrid and in the surroundings of the Community of Madrid the data are dispersed. It is easy to see the profile of the border of the Community of Madrid using the dispersed representation.

> farma<	-read.csv2(file.choose())
> head(f	arma)
х	У
1 440267	4475426
2 440954	4477004
3 441063	4475193
4 442754	4475148
5 441090	4475021
6 437825	4481330
Figure 4: x and y	coordinates of drugstores.



Now we can graphically represent, in figure 5, the location of all the points of all the pharmacies.

> ggplot(farma, aes(x = x, y = y)) + geom_point()

Scaling Data

For a more suitable analysis, the data is converted into a 'tibble'.

Clustering algorithms use distances, and the variables with the largest numerical range will dominate the distance calculation. The summary above shows that this is not a problem for the Pharma dataset, as both x and y are roughly between 37.3263 and 45.45571. Most data analysts will still scale each column of the data to a mean of zero and a unit standard deviation (z-scores). After scaling, most z scores will fall in the range [3,3] (z scores are measured in standard deviations from the mean), where 0 means average.

Discussion

The main problem when using clustering is the selection of the optimal number of clusters

In Figure 6 we can see the representation of the total sum of variance within each cluster, as a function of the cluster number. The jumps from 1 to 2, from 2 to 3, and from 3 to 4 are important, and from 4 or 5 clusters the difference is much smaller. Then, we will try with 3 or 5 clusters, and we will see what results it offers us.

K-Means Clustering

This method implicitly assumes Euclidean distances. We use k=10 clusters and run the algorithm 100 times with random initialized centroids. This gives the best result.

The first results show large differences in cluster sizes, and the cluster centers are one close and one far away.

Cli	ister means:	
	x	У
1	0.13140568	3.6330792
2	0.18069807	0.5302160
3	-3.54615895	-0.6196363
4	-1.21752934	0.4502247
5	-2.36730874	2.0394187
6	-0.75972613	-1.0977784
7	-0.04382947	-0.1793536
8	2.26538312	0.5747282
9	1.01591844	-2.7195404
10	0.79808218	-0.1408803

The variance between the groups and the total is 84%, a high value, but we can improve this value. When checking the assignment of clusters by any pharmacy, it is important to make a comparison in a distribution figure, but first, it is necessary to convert the data into factors.

Given the geometry of the Community of Madrid, it is very complicated to leave a central cluster because it would have a very large number of pharmacies and, in practice, would require a lot of consumption of economic assets. The 4-cluster solution, Figure 7a, divides the central part into two, which facilitates its implementation and viability.





Distance Measurements

Г

Measurement of centroids, indicated by a cross, of each cluster will give us the displacements that autonomous vehicles will have to make. In Figure 7 b we can see the vectors that indicate the maximum distances of the displacements that would have to be made. But these distances must be divided by a value to obtain the average value of the distances.

	a average alotance va	
Movingung and	AVARAGA VALUAA ARA	number of tim

Maximum and average values and number of times to travel					
Green cluster	Max. 60,1Km Med. 41,7Km	300/week			
Purple Cluster	Max. 34,8,1Km Med. 15,4Km	350/ week			
Green/Blue Cluster	Max. 5,1Km Med. 2,5Km	840/ week			
Red cluster	Max. 69,5Km Med. 33,8Km	300/ week			

This would result in total weekly distances that, multiplied by the average number of times the trip is made, would total 30,280 km each week.

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On the other hand, and taking into account the current location of the pharmacy warehouses and the dispersion of the different towns in the Madrid community, the 5-cluster solution shown in Figure 8 seems to be a better solution.

However, the purple cluster, above in Figure 8, could be taken over by green or red clusters.

But since the lighter green cluster intersects the red and blue clusters, pharmacies would potentially be lost, so it seems advisable to take it over by the red cluster, again having a 4-cluster structure.

Light Commercial Vehicle (LCV) vs Zero and Low Emission Vehicle (ZLEV): impact on CO,

A fossil fuel van has two types of pollution, atmospheric and acoustic. Focusing only on its atmospheric CO2 pollution, a mediumsized van or light commercial vehicle (LCV) would have a CO, pollution of 114g/km, according to EU regulations, resulting in 3.5 tons of CO2 emitted each week in the community of Madrid.

The price of an electric vehicle in Spain ranges between €55,000 and €60,000 and has storage capacities of 5 to 11 m3 [17]. As the medicines change depending on the time of year, the baskets or buckets are filled with different pharmaceutical products. Stackable buckets make better use of space and usually have a volume of 35 liters, so more than 100 buckets fit in an LCV of 5 m3. The battery life of an electric vehicle is 150,000 km or 8 years of driving [18]. Then the financial scenario for acquiring an electric LCV is set at 8 years.

Financing of the ZLEV (pure electric)

The Spanish government has the PIVE plan with which it subsidizes the acquisition of an electric vehicle. If the previous vehicle is scrapped, the subsidy is slightly higher, from €8,000 to €9,000. This would lower the costs to a range between €46,000 and €51,000.

For financing, you can choose financing by simply calculating the interest that would be generated in 8 years with that capital or by calculating the net present value, but only with costs, as if it were an investment to calculate what the minimum income should be.

Let us assume that the interest rate of the loan is 5%. We will also assume an average investment of €48,000.

 $C_{c}=C (1+r)^{t}=48000(1+0.05)^{8}=70917.86$

This would then generate interest of €22,917.86, which does not seem to be the most appropriate.

If, instead, we calculate the net present value and use the constant amortization term of a loan using the French method, we obtain the following:

$$a = V / (1 - (1/(1+i))^N)/i) =$$

48000/(1-(1/(1+0,05)8)/0,05=7.426,65

So, the cost would be €59,413.18, i.e. €11,413.18 in interest. Half of the previous case.

If the company obtained at least double "a" we would have positive cash flows of €7,426.65:

NPV=-48000 +
$$\frac{7426,65}{1,05}$$
 + $\frac{7426,65}{(1,05)^2}$ + \cdots + $\frac{7426,65}{(1,05)^8}$ =0

As expected, the value obtained is 0, since the investment is recovered simply by entering the same amount of the constant annualized payment. The residual value of the vehicle at the end of the established period of 8 years has not been considered in the calculation, which it could certainly have, since the batteries could be replaced, if the ZLEV were in working condition, and the unit could continue to be used for more years.

As we can see, a moderate-low income is enough to be able to acquire a Zero and Low Emission Vehicle (ZLEV) in a financial horizon of 8 years and to be able to converge with the fleet replacement intentions declared by the sector [19].

Conclusions

In this section we will express our final contributions based on the following axes: the number of clusters recommended by logistical criteria and territorial convenience in the CAM and the benefit of replacing fleets with non-polluting vehicles from a double perspective, the financial and the environmental.

• Regarding the first, the 4-cluster solution, shown in figure 7a, which divides the central part of the CAM into two more homogeneous areas, is the recommended one because it is the one that best balances the criteria of logistical rationality and facilitation of its implementation and viability by pure electric vehicles.

• Regarding the incorporation and complete replacement of pharmaceutical delivery fleets by ZLEV vehicles, pure electric, non-polluting with 0 CO2 emissions compared to the 114gr of CO2/km set as a maximum by European regulations from 2020 (CE Delft, 2017), it would lead us, in the case analyzed, to a reduction of 179.49 Tm of CO2 per year, in addition to a significant associated reduction in noise pollution not studied.

• Finally, note its complete economic-financial viability with a useful life of 8 years. By calculating the Net Present Value (NPV) and using the constant amortization term of the loan, with the French method, it becomes possible, even without considering the residual value.

Author Statements

Conflicts of Interest

All other authors declare that they have no conflicts of interest.

Acknowledgment

We sincerely thank the Community of Madrid (CAM) and the National Geographic Institute of Spain for their collaboration.

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