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A Descriptive Cross-Sectional International Survey of Pack Size Restriction

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Availability of Paracetamol Sold Over-the-Counter in Europe: A Descriptive Cross-Sectional International Survey of Pack Size Restriction

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Abstract
Due to the risk of hepatotoxicity when excessive amounts of paracetamol are consumed, Poisons Information Centers (PICs) frequently receive paracetamol-related enquiries. This study examined how widely pack size restrictions of paracetamol sold over-the-counter

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have been implemented in Europe and also availability of paracetamol through non-pharmacy outlets and their possible associations with frequency of poisoning enquiries.

A cross-sectional European multicentre questionnaire study was performed using a questionnaire to identify the extent and nature of paracetamol pack size restrictions, non-pharmacy outlet sales and the frequency of paracetamol-related enquiries to PICs.

In total, 21 European countries participated. All PICs provided telephone hotline services.

In 14 (67%) countries, pack size restrictions had been implemented in pharmacies (range: 8-30 grams). No significant difference (median difference 0.7%, p-value=0.36) was found when comparing median frequencies of paracetamol-related enquiries in countries with pack size restriction to countries without restrictions. A significantly lower median frequency of paracetamol-related enquiries was found in countries without non-pharmacy outlet sales compared to those with such sales (median difference 2.2%, p = 0.02).

Pack size restrictions on pharmacy sales of paracetamol have been implemented in two thirds of examined countries. There was no difference in the proportion of paracetamol-related enquiries to PICs among countries with and without pack size restrictions. However, a lower rate of paracetamol-related enquiries was noted in countries where paracetamol was not available in non-pharmacy outlets.

Suicidal behaviour constitutes a global health burden with close to one million deaths annually and 10-40 times as many episodes of self-harm [1]. In European countries, poisonings account for the major part of hospital-presenting deliberate self-harm, and analgesics, especially paracetamol, are frequently used for intentional self-poisoning [2-5].

Mild analgesics including paracetamol are sold in all European countries with or without prescription and often in large quantities. Yet, intentional and accidental self-poisoning with especially paracetamol represents a significant healthcare problem [4,6,7]. The proportion
of paracetamol-related poisonings related to all poisonings varies among European emergency departments; ranging from 4.5 % as reported in Spain [8] to 12% in Norway [9] and 40-44% in the UK over the past decades [10]. Poisons Information Centres (PICs) which answer enquiries, including those related to paracetamol, are established in most European countries [11]. A comparison of PICs worldwide showed that paracetamol was among the 20 most frequent agents for which enquiries were made [12]. However, the association between paracetamol sold over-the-counter (OTC) in pharmacies and non-pharmacy outlets and number of enquiries to PICs is sparsely described and with conflicting findings [13,14]. A British report found no decrease of paracetamol-related enquiries when comparing frequencies before and after implementation of the British pack size restriction on paracetamol [15]. However, an Irish report showed a decrease in severity of paracetamol poisonings and number of tablets taken, as recorded from paracetamol-related enquiries, after the Irish pack size restriction had been introduced [16]. During 2010-2013, the Swedish Medical Agency reported a marked increase in paracetamol-related enquiries, arguing that this was related to the introduction of sales in non-pharmacy outlets in November 2009 [13]. This was supported by an earlier Swedish report that related a 158% increase (50% within the first three years) in the number of paracetamol-related PIC enquiries to the same legislative change [17].

Paracetamol may be hepatotoxic when ingested in doses exceeding daily recommendations [7,18,19]. Gulmez and colleagues noted that a liver transplant was needed in 0 - 52% of ALF cases due to overdose by paracetamol in a sample mainly from the UK and Ireland. The same report revealed that nearly 97% of all ALF overdose cases were due to paracetamol poisoning [20], though varying across Europe [21]. The relatively low case fatality rate is partly explained through high standards in clinical practice [22], including treatment with the antidote, N-acetylcysteine [23].

Suicidal behaviour is a complex phenomenon, with suicidal ideation and actions fluctuating over time [24]. Impulsive suicidal behaviour, which is particularly prevalent among the young, implies that the person would tend to use means available in close proximity, e.g. agents available in the household [25,26]. One suicide preventive measure is to restrict access to potentially toxic drugs like paracetamol [27-29] and restrictions on pack sizes of
mild analgesics including paracetamol sold OTC have been introduced in several European countries [30]. A structured overview of the availability of paracetamol tablets OTC and its association with self-poisoning was published in 2000 for European countries [4]. However, an update is due. The primary aim of the present study was to gain an updated overview of restrictions on paracetamol sold OTC in pharmacy and non-pharmacy outlets in Europe. Secondly, we wanted to investigate the association between frequency of paracetamol-related enquiries to PICs and availability of the drug.

Methods

Design and setting

We conducted a European multicentre study in a cross-sectional design during 2015 and 2016 describing the availability status of paracetamol sold OTC in European pharmacies and other retail outlets.

PICs in all European countries were contacted using the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) member lists. The EAPCCT is a scientific association with individual members rather than countries. Currently, it includes members from 29 countries, covering all major countries in Europe.

Data

A detailed survey questionnaire was developed and distributed via email to all current members by the EAPCCT secretary during March 2015 (see Appendix). Responses were returned directly via e-mail to the corresponding author, and data were entered into an electronic database. Responses were reviewed by two researchers or through follow-up enquiries to the respective PIC in order to clarify unclear information. Where we received several responses from the same country, responders were contacted with the aim of settling potential differences. Responses with national level data were preferred.

The survey included questions regarding: description of PIC; national availability of paracetamol tablets; pack size restrictions in pharmacies and non-pharmacy outlets; number of tablets and grams sold OTC and presence of blister package products; services
provided by the local PIC (calls, hotline, web contacts or ward activity); annual numbers of paracetamol-related enquiries as well as total number of enquiries for the years 2011-2013; risk assessment of poisoning enquiries using the standardized Poisoning Severity Score, as introduced by EAPCCT in 1990 [31]; access to hospital records, discharge letters; and other services, such as Ministry consultancy, educational activities or surveillance functions.

Missing data
A reminder was dispatched five months after the initial questionnaire by the EAPCCT general secretary. PICs in non-responding countries were followed up with emails. Lastly, aggregate data on enquiries to PICs were downloaded from the website of the UK National Poison Information Services since no personal reply was achieved from the UK, and this procedure was recommended by leading British toxicologists [32].

Analysis
Descriptive analysis was supplemented by non-parametric tests of differences. A normal distribution could not be assumed with respect to mean proportions of paracetamol-related enquiries of all poisonings to PICs due to significant outliers observed in data from two countries. This meant that calculations were based on medians. This also applied to the calculation of rates where a normal distribution of either observed or estimated means could not be assumed; hence not supporting Poisson regressions. The Wilcoxon and Mann-Whitney U test of differences, respectively, were applied to determine differences among countries with and without pack size restrictions, as well as among those with and without non-pharmacy outlet sales.

Ethical considerations
Ethical approval was not required as no person-level data were collected.

Results
In total, 21 European PICs or EAPCCT members responded. According to the EAPCCT website, there are currently PICs in 29 European countries. Assuming that all members in the possible 29 European countries had received the survey, the country-based response
rate was 72.4%. We obtained responses from 18 PICs covering nationwide information, while three PICs provided information at a sub-national level (Munich, Germany; Lodz, Poland; and Moscow, the Russian Federation).

Pack size restrictions
In 14 (67%) of the responding countries, pack size restrictions had been implemented in pharmacies (range: 8 to 30 grams in blister packages) (Table 1). Countries where pack size restrictions had not been introduced were predominantly Eastern European (Slovakia, Lithuania, Croatia, Czech Republic, Poland (Lodz) and the Russia Federation (Moscow)). In 12 (57%) countries, mild analgesics including paracetamol were not available in non-pharmacy outlets. Respondents from all countries confirmed that larger quantities of paracetamol were available to patients through prescription from their primary care doctor.

Enquiries to PICs about poisonings
Only countries where information on annual paracetamol-related enquiries and total number of enquiries (n= 17) had been reported were included in further analyses. Rates of enquiries per 100,000 inhabitants from the public were presented for the year 2013 for countries providing these services (n=18) (Table 2).

Despite the fact that pack size restrictions have been implemented in the UK, Ireland and Sweden, a larger proportion of paracetamol-related enquiries was noted in these countries compared to others (Table 2). Yet, at the same time, mild analgesics including paracetamol were available in non-pharmacy outlets. Most countries where paracetamol was sold in non-pharmacy outlets had a proportionally higher percentage of annual mean number of paracetamol-related enquiries when compared to countries with no such sales. France was an exception to this. Two significant outliers regarding mean paracetamol-related enquiries were identified (Table 2), leading to the necessity for using non-parametric tests of differences for median proportions of paracetamol-related enquiries, presented in Table 3. No significant difference in paracetamol-related enquiries were found among countries with pack size restriction (range 1.1% to 16.1%) and countries without pack size restriction (range 1.7% to 5.6%); median difference 0.7%, p = 0.36. However, a significant difference was noted for median proportions of paracetamol-related enquiries among countries with no
non-pharmacy outlet sales (range 1.1% to 5.3%) and those with non-pharmacy outlet sales (range 1.9% to 16.1%); median difference 2.2%, p = 0.02 (Table 3).

We found a shift in impact of paracetamol-related enquiries when calculated as rates per 100,000 inhabitants. The rates ranged between 1.1 in Croatia to 39.7 per 100,000 inhabitants in Sweden; implying that Sweden had the highest rate of enquiries. The non-parametric test revealed that the mean rate of paracetamol-related enquiries to PICs was higher in countries with pack size restrictions than in those with no pack size restrictions (p=0.027) (Table 3). Also, a higher mean rate of paracetamol-related enquiries per 100,000 inhabitants was noted in countries with non-pharmacy outlet sales of paracetamol when compared to those with no non-pharmacy outlet sales (p=0.019).

In three of 21 countries (Slovenia, The Netherlands and the UK), PIC services were provided for clinicians only. In spite of the vast majority of countries providing services for both clinicians and the public, we found large differences in rates of public enquiries among countries (Table 2). The rates varied from 0.7 in Slovakia to 609.5 per 100,000 inhabitants in Belgium. All responding PICs provided phone hotline services, while 11 (55%) offered personal consultations and 13 (65%) supported web-based enquiries. Action cards (stepwise information on risk assessment and treatment guidelines) were available from five of the PICs (26%), while other services were supplied by 16 of the centres (80%). These covered: special ward facility, insurance or Ministry consultancy, educational activities and surveillance functions. Five centres (24%) were able to systematically access hospital records, including information on diagnosis codes, while nine centres (43%) had access to discharge letters. Routine risk assessment of the level of paracetamol poisoning was performed by 17 of the PICs (77%), of which 8 (36%) applied the Poisoning Severity Score, the severity grading scale suggested by the EAPCCT [31].

Discussion

This is, to our knowledge, the first study to examine the impact of pack size restrictions and non-pharmacy availability of paracetamol in Europe based on data from European PICs. Pack size restrictions on pharmacy sales of paracetamol have been implemented in two thirds of
the examined countries. There was no difference in the proportion of population-based paracetamol-related enquiries (per 100,000 inhabitants) to PICs among countries which had and had not implemented pack size restrictions. However, there was a higher population-based rate of paracetamol-related enquiries in countries where mild analgesics including paracetamol were sold in non-pharmacy outlets.

The fact that level of enquiries seemingly did not depend on whether pack size restrictions had been introduced might seem surprising, especially considering the strong evidence from the UK that pack size restrictions were linked to substantial reductions in deaths from paracetamol poisoning [33]. However, our findings may reflect a greater pressure to reduce pack sizes in countries in which the incidence of paracetamol overdoses is high.

The finding that paracetamol-related enquiries are greater where non-pharmacy sales are permitted is supported by a Czech study in 2004 where the number of enquiries concerning pharmaceuticals including paracetamol and ibuprofen over a five-year period rose following a legislative change allowing sales in non-pharmacy outlets [34]. In Norway, sale of paracetamol in non-pharmacy outlets was introduced in 2003. A subsequent study showed no difference in number of hospital contacts for paracetamol overdoses when comparing the two years before and after the legislative change, although an increase in the number of paracetamol-related enquiries to PICs was noted. However, the authors concluded that the severity of paracetamol poisonings had decreased [14]. In Sweden, sales outside pharmacies were introduced in 2009; during the following four years, a 40% increase in paracetamol-related poisonings was noted using national register data on hospital admissions and causes of death [35]. A similar increase in paracetamol-related enquiries to PICs was noted [13]. The increase observed in Sweden was associated with the liberalisation and as a direct consequence of this, sales of paracetamol as regular tablets were withdrawn from non-pharmacy outlets in 2015, leaving only effervescent tablets on the market (that were not associated with an elevated toxicity risk) [13]. One should think that the Swedish approach of pack size restrictions in pharmacies and no sales in non-pharmacy-outlets might ensure that paracetamol are available in a safer and controlled manner. However, the total number of PIC consultation related to paracetamol poisoning has continued to increase in Sweden [36]. Long-term studies are needed to determine the effect of the intervention, possibly using
data on hospital admissions for poisonings. In Denmark, another legislative change prior to pack size restriction was implemented in March 2011. This legislation prohibited sales of mild analgesics including paracetamol to minors below 18 years of age. However, it is not known if this had an impact on hospital contacts due to overdose.

We found that the PICs in the UK and Ireland had particularly high frequencies of paracetamol-related enquiries (16% and 15% of all inquiries, respectively) compared to the other participating countries. This matches national reports stating that paracetamol intoxication is the most common poisoning in the UK and Ireland [32,37]. It is also well documented that rates of self-harm by overdose of paracetamol, recorded as hospital contacts in the UK and Ireland are substantially higher [38] than in other European countries [2].

Examination of the impact of paracetamol-related enquiries when based on population size (rates per 100,000 inhabitants) changed the picture. The highest rates were then found in Sweden, with a mean rate of 38.7 per 100,000. This finding is clearly in line with the above-mentioned most recent legislative decision to withdraw sales of regular paracetamol tablets from all non-pharmacy outlets [13]. Future Scandinavian studies investigating the impact of the ban on sales from non-pharmacy outlets on population-based hospital and PIC data also taking prescription patterns into account will provide important information for public health policy makers.

One essential difference in PICs across Europe was the target group in that 18 (86%) provided services for both clinicians and the public, whereas in the remaining three countries PICs only provided services for clinicians. Typically the latter types of PICs will refer public enquiries on to GPs. Among PICs which provided services to both clinicians and the public, rates of public enquiries differed significantly possibly suggesting different levels of public awareness. A steady increase in the number of public enquiries has been noted by PICs [16,39]. Some PICs use public awareness campaigns and social media initiatives to increase public awareness [40].
We found that among the responding countries, it seemed that pack size restriction was accepted as a suicide prevention strategy, in spite of very few national evaluations of this initiative [4,41]. Evidence in favour of the pack size restriction has been reported through significantly reduced paracetamol-related deaths and also referrals for liver transplantation [41].

Strengths and Limitations

Data were provided by experts in the field of toxicology and representatives from European PICs with access mainly to national level enquiry data. Due to the close collaboration with EAPCCT, which distributed the questionnaire and e-mail reminders, an estimated response rate of 72% was obtained. This contrasts previous investigations involving EAPCCT members, which have reported response rates of less than 30% [4,12]. No uniform, international data sources are available in this area; hence, the current data collection can be viewed as unique.

Although a structured questionnaire was used, we obtained heterogeneous replies, and answers from several PICs were incomplete. The lack of response from larger countries, such as Spain and Portugal, is unfortunate. It was not possible to examine whether legislative rules regarding number of packages allowed in single sales played a role due to lack of responses. Availability in households of paracetamol-related drugs does not solely depend on availability OTC; a substantial share of the population will have obtained the drugs through prescription, which was not feasible to assess in this study.

It would have been preferred to have complete data on sales of paracetamol. However, this would not have been feasible without having to compromise the number of reporting countries.

The difference in service provision between accepting enquiries from clinicians only or from both clinicians and the public is unfortunate when examining enquiries as a surrogate outcome; we have met this limitation by calculating rates of enquiries from the public for the year 2013 where data were obtained. Only three countries did not take public enquiries,
namely Slovenia, The Netherlands and the UK. It could be argued that their enquiries might be related to more severe cases; however, it was not feasible to address level of severity in this survey, such as through a poisoning severity score.

The term ‘paracetamol-related enquiries’ might have been differently interpreted by responders, ranging from mild poisonings to severe cases. It might also have been unclear whether multi-drug poisonings should be included or not. This level of detail could unfortunately not be addressed in the questionnaire. Although self-poisonings with paracetamol is frequent in European countries, there is likely to be variation in self-harming methods among countries [2,4]. Hence, it would be fair to state that not only restrictions but also cultural habits may influence the pattern in methods used for self-harm. Future analysis would benefit from national data on hospital admissions for poisonings as well as other relevant clinical outcomes.

To conclude, in most European countries, clinicians and the public have access to treatment advice on paracetamol-related poisonings through PICs. In the majority of examined countries, pack size restrictions have been implemented for mild analgesics including paracetamol sold OTC in pharmacies. Countries with no pack size restriction in pharmacies and no sales in non-pharmacy outlets had fewer paracetamol-related enquiries to PICs. One conclusion would be that pack size restriction has no influence on the number of paracetamol poisoning, whereas not selling paracetamol OTC has. However, the lack of significant difference in the proportion of enquiries among countries with no pack size restriction and those with pack size restriction indicates a need for further research using national data and toxicity-related outcomes. The higher rate of paracetamol-related enquiries in countries where mild analgesics including paracetamol were available in non-pharmacy outlets could suggest that more restrictive measures might be advisable.

Conflict of interest
None.
Reference List


**Table 1** European PICs, their year of establishment, pack size restriction on paracetamol in pharmacies, and sales in non-pharmacy outlets by country

<table>
<thead>
<tr>
<th>Country</th>
<th>PIC</th>
<th>Year of establishment of PIC</th>
<th>Area of coverage</th>
<th>OTC Pharmacy sales (gram)</th>
<th>Non-pharmacy outlet sales (gram)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Countries with restriction (n=14)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Austria</td>
<td>Poisons Information Center Vienna</td>
<td>1975</td>
<td>National</td>
<td>30</td>
<td>No sale</td>
</tr>
<tr>
<td>Belgium</td>
<td>Anti-Poison center of Belgium</td>
<td>1963</td>
<td>National</td>
<td>10</td>
<td>No sale</td>
</tr>
<tr>
<td>Denmark</td>
<td>Information Center Danish Poison</td>
<td>2006</td>
<td>National</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>France</td>
<td>Toxic vigilance Coordination Committee and Association of French Poison Centers</td>
<td>1999</td>
<td>National</td>
<td>8</td>
<td>No sale</td>
</tr>
<tr>
<td>Finland</td>
<td>Finnish Poison Center</td>
<td>1961</td>
<td>National</td>
<td>15</td>
<td>No sale</td>
</tr>
<tr>
<td>Germany/Munich</td>
<td>Poison Information Center Munich</td>
<td>1968</td>
<td>Regional</td>
<td>10</td>
<td>No sale</td>
</tr>
<tr>
<td>Ireland</td>
<td>National Poison Information Center Ireland</td>
<td>1966</td>
<td>National</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Italy</td>
<td>Florence Poison Center &amp; Pavia Poison Control Center</td>
<td>1991</td>
<td>National</td>
<td>15</td>
<td>No sale</td>
</tr>
<tr>
<td>Norway</td>
<td>Norwegian Poisons Information Center</td>
<td></td>
<td>National</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Slovenia</td>
<td>Poison Control Centre, Division of Internal Medicine, Ljubljana</td>
<td>1973</td>
<td>National</td>
<td>10</td>
<td>No sale</td>
</tr>
<tr>
<td>Sweden</td>
<td>Poison Information Center Sweden</td>
<td>1960</td>
<td>National</td>
<td>10</td>
<td>No sale*</td>
</tr>
<tr>
<td>Switzerland</td>
<td>Tox Info Suisse</td>
<td>1966</td>
<td>National</td>
<td>8</td>
<td>No sale</td>
</tr>
<tr>
<td>UK</td>
<td>National Poison Information Services England (Toxbase 1982)</td>
<td>1962</td>
<td>National</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td><strong>Countries without restriction (n=7)</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Country</th>
<th>Center/Center of Medical and Biological Agency</th>
<th>Year</th>
<th>Type</th>
<th>Quantity</th>
<th>Sale Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Croatia</td>
<td>Poison Control Center Zagreb</td>
<td>1970</td>
<td>National</td>
<td>Unlimited</td>
<td>No sale</td>
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<tr>
<td>Czech Republic</td>
<td>Toxicological Information Center of Czech Republic (TIC)</td>
<td>1964</td>
<td>National</td>
<td>Unlimited</td>
<td>6</td>
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<tr>
<td>The Netherlands</td>
<td>Dutch Poison Information Center</td>
<td>1959</td>
<td>National</td>
<td>Unlimited</td>
<td>No sales</td>
</tr>
<tr>
<td>Lithuania</td>
<td>Poison Information Bureau</td>
<td>2012</td>
<td>National</td>
<td>Unlimited</td>
<td>No sale</td>
</tr>
<tr>
<td>Poland/Lodz</td>
<td>Poison Information Center</td>
<td>1967</td>
<td>Regional</td>
<td>Unlimited</td>
<td>6</td>
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<tr>
<td>Russian Federation/Moscow</td>
<td>Research and Applied Toxicology Center of Medical and Biological Agency</td>
<td>1993</td>
<td>Regional</td>
<td>Unlimited</td>
<td>Unlimited</td>
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<tr>
<td>Slovakia</td>
<td>Research and Applied Toxicology Center of Medical and Biological Agency</td>
<td>1968</td>
<td>National</td>
<td>Unlimited</td>
<td>No sale</td>
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</tbody>
</table>

* In 2015, Sweden withdrew sales of mild analgesics including paracetamol (10 g) from non-pharmacy outlets sold as regular tablets leaving only effervescent tablets on the market.
<table>
<thead>
<tr>
<th>Pack size restriction in pharmacy</th>
<th>Sales restricted to pharmacies</th>
<th>Country</th>
<th>Mean percent of paracetamol-related enquiries of all poisonings (%)</th>
<th>Overall rate of enquiries per 100,000 inhabitants and (paracetamol-related enquiries) 2011-2013</th>
<th>Rate of public enquiries per 100,000 inhabitants in 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pack size restriction in pharmacy</td>
<td>Sales restricted to pharmacies</td>
<td>Italy</td>
<td>2.7</td>
<td>61.0 (1.66)</td>
<td>10.7</td>
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<tr>
<td>Available in non-pharmacy outlets</td>
<td></td>
<td>France</td>
<td>5.3</td>
<td>289.6 (15.45)</td>
<td>170.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Belgium</td>
<td>2.6 **</td>
<td>714.5 (12.55 **)</td>
<td>609.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slovenia¹</td>
<td>3.9 **</td>
<td>83.9 (3.23 **)</td>
<td>Clinicians only</td>
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<td></td>
<td></td>
<td>Austria</td>
<td>1.1</td>
<td>283.7 (3.06)</td>
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<td></td>
<td>Iceland</td>
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<td></td>
<td></td>
<td>Switzerland</td>
<td>3.4</td>
<td>456.0 (15.39)</td>
<td>296.2</td>
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<td></td>
<td></td>
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<td>Missing *****</td>
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<td></td>
<td>Finland</td>
<td>3</td>
<td>566 (17.12)</td>
<td>14.5</td>
</tr>
<tr>
<td>No pack size</td>
<td>Sales restricted to</td>
<td>Ireland</td>
<td>16.1 *</td>
<td>212.8 (34.14)</td>
<td>59.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Norway</td>
<td>3.4</td>
<td>792.2 (27.03)</td>
<td>504.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sweden</td>
<td>4.7</td>
<td>854 (39.68)</td>
<td>606.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>UK¹</td>
<td>14.9 *</td>
<td>64.9 (9.69)</td>
<td>Clinicians only</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Denmark</td>
<td>5.4</td>
<td>380.4 (20.67)</td>
<td>173.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slovakia</td>
<td>3.4</td>
<td>77.7 (2.60)</td>
<td>0.7</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>restriction in pharmacy</th>
<th>pharmacies</th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lithuania</td>
<td>1.7</td>
<td>77.5 (1.32)</td>
<td>45.5</td>
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<td>Croatia</td>
<td>2.7</td>
<td>40.3 (1.08)</td>
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<tr>
<td>Available in non-pharmacy outlets</td>
<td>Czech Republic</td>
<td>2.7</td>
<td>153.3 (3.58)</td>
<td>61.6</td>
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<td>Moscow (Russian Federation)</td>
<td>1.9***</td>
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<td>Missing *****</td>
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<td></td>
<td>The Netherlands ¹</td>
<td>5.6</td>
<td>264.3 (14.79)</td>
<td>Clinicians only</td>
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<td>Poland (Lodz)</td>
<td>5</td>
<td>Missing *****</td>
<td>Missing *****</td>
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</tbody>
</table>

* Significant outliers of mean frequencies
** Data only available for 2012 and 2013
*** Data only available for 2013
**** Data not available, hence Iceland not included in the analysis.
***** Only regional data available
****** Only city data available

¹ In Slovenia, The Netherlands and the UK PICs provide services for clinicians only
<table>
<thead>
<tr>
<th>Pack size restriction in pharmacies</th>
<th>Median percent of paracetamol-related enquiries of all poisonings 2011-2013 (%) (range)</th>
<th>Median difference (%)</th>
<th>p-value&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Rate of paracetamol-related enquiries per 100,000 inhabitants</th>
<th>Mean difference (95 % CI)</th>
<th>p-value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes (n = 13)</td>
<td>3.4 (1.1 – 16.1)</td>
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<td>16.64</td>
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<tr>
<td>No (n = 7)</td>
<td>2.7 (1.7 – 5.6)</td>
<td>0.7</td>
<td>0.362</td>
<td>-11.97</td>
<td>0.027*</td>
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<tr>
<td>Packages available in non-pharmacy outlets</td>
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<td>(-21.25 to -2.68)</td>
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<tr>
<td>Yes (n = 9)</td>
<td>4.9 (1.9 – 16.1)</td>
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<td>21.37</td>
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<tr>
<td>No (n = 11)</td>
<td>2.7 (1.1 – 5.3)</td>
<td>2.2</td>
<td>0.02*</td>
<td>7.35</td>
<td>(-26.39 to -1.66)</td>
<td>0.019*</td>
</tr>
</tbody>
</table>
Based on countries where regional or national data were available.

Using the Wilcoxon test and Mann-Whitney U test, respectively

* Significance level 0.05