Paracetamol dosing errors in people aged 12 years and over: an analysis of over 14 000 cases reported to an Australian Poisons Information Centre

Running Header: Paracetamol dosing errors reported to an Australian Poisons Information Centre
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SUPPLEMENTARY MATERIALS:

Supplementary Methods:

Definitions

The following definitions and thresholds are used throughout the paper:

- **Therapeutic dose =** 2 x 500 mg tablets, 2 x 665 mg tablets or 1 x 500 mg tablets + 1 x 665 mg tablets for individuals weighing >50 kg or 15 mg/kg for individuals weighing ≤50 kg
- **Therapeutic interval** ≥4 hours for immediate release (IR) formulations or ≥6 hours for modified release (MR) formulations
- **Maximum daily dose =** 4 g per 24 hours
- **Dosing error:** Taking paracetamol for a therapeutic purpose at either a dose or interval that does not align with the above recommendations or via the wrong accepted route of administration or when paracetamol is given to an individual whom it is not intended for.
- **Repeated supratherapeutic ingestion (RSTI):** Patients who ingest paracetamol excessively for therapeutic purposes or who take paracetamol at therapeutic doses but develop symptoms of liver injury (as described by the Australian and New Zealand guidelines [1])

Additional information on data cleaning and extraction steps:

Exclusion criteria

Calls were excluded from further analysis if they met any of the following criteria:

- If a dose was taken ≤15 minutes before the therapeutic interval this was not considered an error
- If 1 tablet of any strength was taken and then repeated before the therapeutic interval this was not considered an error unless it was repeated to become more than a therapeutic dose
- If the ingestion was a deliberate self-poisoning or not taken in error for therapeutic use
- If the ingestion was due to intentionally abusing any opioids in the preparation (for combination products)
- If the reason for ingestion was clearly impulsive such as after an argument unless being used therapeutically such as for sedation
- Ingestion of expired products unless taken supratherapeutically or at a reduced interval
- If there was no error and the hospital determined the presenting symptoms were not due to ingestion of paracetamol
- If there was unclear confirmation of paracetamol use AND results from medical records did not support its ingestion
- Exposures for products that do not include or were accidentally coded as containing paracetamol

Exposures

NSWPIC often receives follow up calls regarding one exposure (termed recalls, e.g. a call from a family member, then a hospital clinician). These were only counted once, however any outcome data available in recall records was taken into account for that exposure for the 2021 in-depth screening. Occasionally, one call will contain information about multiple exposures (e.g. two teenagers receiving excessive paracetamol due to a dosing error by parents). In these cases, that call record was split to count two exposures.

This data is unlinked and thus an individual could potentially appear in the dataset more than once if they had several exposure events.

Age classifications

NSWPIC collects both age category (coded field) and age (free text field usually containing exact age but sometimes containing an estimate or a range). Ages were screened and those with a recorded age were placed into the correct category if it was initially incorrect. For those with an age range listed in the free text only, the middle value was used as an approximation. If an age was recorded as approximate it was simply changed to that age. Those with an unknown age were screened to see if age was mentioned in the free text. Age was also corrected if it was missing or incorrect during medical record screening.

Sex classifications

Sex classifications were updated if incorrectly categorised (eMR considered correct). Those with an unknown coded sex/gender were screened to see if this was mentioned in the free text.

Paracetamol product type involved

The paracetamol involved includes any form of paracetamol taken within a 24-hour period that includes the error. Each brand/formulation of paracetamol mentioned was included as a separate row to allow for analysis. If additional rows were added from a recall (as new information came to light) then the original exposure call was adjusted. The use of more than one brand of the same formulation was included as a separate row to allow for analysis of multiple paracetamol-containing products.

Product categorisation was checked and fixed if necessary. Free text brand/product information was categorised into broad product types: *immediate release (single ingredient formulations), modified release (single ingredient formulations), combinations with opioids, cold and flu preparations, combinations with ibuprofen/NSAID, combinations with an opioid and antihistamine, combinations with caffeine, other combinations*. Any categorisation errors made in the original call record were corrected for analysis. Some records mentioned a specific brand however specified ingredients which did not match current formulations – in that case the product was categorised according to the ingredients listed.

NSWPIC codes both IR, MR and intravenous (IV) paracetamol under the same group 'Paracetamol' and so screening was done to separate these three groups. Immediate release paracetamol includes a variety of formulations including tablets, capsules, liquid and suppository formulations. Modified release paracetamol includes only controlled release tablets. Where the product name only stated 'paracetamol' without giving a strength or formulation it was assumed to be IR paracetamol. Similarly with the brand 'Dimetapp', a cold and flu medication, various records quoted it under different strengths. Where the product name gave no strength, it was assumed to be 300 mg of paracetamol. With the brand 'Lemsip' it was assumed to be a 500 mg sachet unless stated otherwise and 'Lemsip Max' was considered to be a 1000 mg sachet.

Some records separated cold and flu tablets into two rows for day and night tablets such that they represented two formulations. However due to inconsistencies and the fact that they are often sold together in a pack, in the 2021 detailed data clean they were counted as a single formulation only and were not considered as having taken multiple paracetamol-containing products.

For the entire cohort the use of multiple paracetamol-containing products was calculated by counting how many paracetamol-containing substance rows were present for an exposure, as generally each paracetamol product recorded is separated into a different row. For the 2021 cohort this was manually entered into a separate column during the screening process.

Schedule Status

In Australia medicines fall within different categories depending on how tightly the sale or supply is regulated [2].

Unscheduled
- Unscheduled products are those which have no conditions on their sale.

Schedule 2
- Schedule 2 products are known as 'Pharmacy Medicines' and are generally available to the public within pharmacies without restrictions. Other businesses can apply to sell Schedule 2 products but only if they are licenced.

Schedule 3
- Schedule 3 products are known as 'Pharmacist Only Medicines' and are kept within the dispensary area of a pharmacy. These medicines do not require a prescription however to access them an individual must personally approach a pharmacist who will determine whether the medication can be supplied.

Schedule 4
- Schedule 4 products are known as 'Prescription Only Medicines' and are kept within the dispensary area of a pharmacy. These medicines can only be supplied with a prescription.

International Product

- Any medicines that have been coded as an international product are to the best of our knowledge, products that are not supplied to the Australian public.

Handling/Disposition

Handling/Disposition represents either the management advice (e.g. referral to hospital) or the current management of the case (for those already in hospital). In the former case, this is the decision by the specialist in poisons information (SPI). This coded field was input at the time of the initial call and was not altered during data extraction.

Symptoms present at time of call to PIC (coded field)

Symptoms present are based off the information given to the SPI at the time of the call. This was not altered by researchers.

Indication for paracetamol use

Indications were listed under what was recorded in the free text or during medical record screening. If no indication was mentioned for paracetamol use this was left as unknown. Dental work was classified as any form of tooth extraction or dental procedures such as the fitting of braces.

Referred to/managed in hospital ('Hospital group') vs Managed at home/in community ('Community group')

For the entire cohort exposures with a Handling/Disposition code classified as 'in hospital' or 'hospital refer' were considered the 'hospital group'. All other Handling/Disposition codes were considered the 'community group'.

However, some of these dosing errors also involved other substances (e.g. nursing home errors involving all of a residents medicines). In addition, some people present to hospital unnecessarily. The in-depth screening in 2021 was able to better represent the management of a case and the burden on the hospital system *attributable to paracetamol*.

Exposures in 2021 were categorised into the 'hospital group' and 'community group', using the Handling/Disposition code in combination with the free text case notes field. Exposures were classified as the hospital group only if the SPI deemed the individual to need hospital investigations or management specifically for the paracetamol ingestion. If the Handling/Disposition code was 'In hospital' at the time of the call but without any apparent need this was not considered hospital management and the individual would fall into the community group. If an exposure involved multiple medicines (e.g. dosing errors with dose administration aids) and hospitalisation was required due to other medications but not paracetamol, this was considered the community group.

Error classifications

Paracetamol dosing errors were further classified as follows:

Acute incorrect dose
- When an individual has taken a supratherapeutic dose only once
- If a dose was initially taken and then repeated <15 minutes later (totalling greater than a therapeutic dose) this was considered an acute incorrect dose

Acute interval error
- When an individual has taken a dose at a reduced interval only once
- If a dose was initially taken and then repeated ≥15 minutes later (totalling greater than a therapeutic dose) this was considered an acute interval error

Acute dose and interval error
- When an individual has taken a supratherapeutic dose AND taken a dose at a reduced interval only once
- These errors may have occurred separately over the period of error or may have occurred together as a once off error

Repeated incorrect dose

- When an individual has taken a supratherapeutic dose more than once but at a normal interval

Repeated interval error

- When an individual has taken a dose at a reduced interval more than once

Repeated dose and interval error

- When an individual has taken a supratherapeutic dose more than once AND taken a dose at a reduced interval more than once during a period of error

Complex RSTI

- When the dose taken was clearly supratherapeutic but could not clearly fit into any of the above groups

Wrong patient

- When an individual was given another person's medication by a third party (e.g. carer, nurse)
- This does not include if an individual accidentally takes another person's medication by their own free will

Weight 50 kg or less without dose adjustment

- When no other form of error occurred but an individual weighing ≤50 kg took or was given a supratherapeutic dose for their weight

Correct dose and interval but over maximum daily dose

- When an individual takes a therapeutic dose at the correct interval however exceeds 4 grams per day (e.g. someone who takes paracetamol four-hourly can reach 6 grams in a 24 hour period)

Wrong route of administration

- When an individual administers a product not in the way it was intended (e.g. ingestion of a suppository)

No documented therapeutic error but developed toxicity

- When an individual has reportedly taken therapeutic doses and none of the above errors have occurred but the individual has developed symptoms of toxicity

Dose within a 24 h period

The dose of paracetamol was calculated as the maximum taken within a 24 hour period. If the dose was presented as being taken over a period longer than 24 hours it was then recalculated to produce an average 24 hour dose. If an approximate range was given the highest value was used. If paracetamol was also being taken therapeutically outside of the error this was added towards the total daily dose (consistent with how RSTI risk assessment is performed). If the caller was unsure if IR or MR paracetamol was used the dose was recorded as if the ingestion was IR paracetamol. If there were dose discrepancies in either the NSWPIC call or medical record screening the worst-case scenario was used. If the dose was quoted as > a value e.g. >4 g the sign was dropped to allow for analysis.

Duration of error

If only one error occurred, this was classified as a once off error. Otherwise, if more than one error occurred the duration was calculated from the first error to the nearest half day. If a large amount of paracetamol was taken over an hour this was considered a once off error as it likely occurred in the same manner listed under 'Acute Incorrect Dose'.

If an approximate range was given the highest value was used. If it was unclear at what point the error started whole days were assumed. If the error was coded as 'Correct Dose and Interval but over Maximum Daily Dose' whole days were used. If the individual had taken paracetamol in error for a period of time but then started taking paracetamol therapeutically again only the period of error was counted in the duration.

If there were duration discrepancies in either the NSWPIC call or medical record screening the worst-case scenario was used. If 'days' were the supposed duration this was counted as 2 days unless specified, for 'weeks' this was counted as 14 days unless specified, for 'months' this was counted as 60 days unless specified, for 'years' this was counted as 730 days unless specified. If the duration was quoted as > a value eg >2 days the sign was dropped to allow for analysis.

The RSTI categories (≥10 g/24 h, ≥12 g/48 h and ≥4 g for >48 h with related symptoms) are derived from the definitions listed in the Australian and New Zealand paracetamol poisoning guidelines Box 1 [1].

The 'Dose within a 24 hr period' and 'Duration of error' as well as the 'Symptoms present at time of call to PIC (coded field)' were used to classify the exposures as follows

1. Ingestion of 10g or more in a single 24 hour period

2. Ingestion of 12g or more over a single 48 hour period
3. Ingestion of a daily therapeutic dose or greater for more than 48 hours PLUS have symptoms (abdominal pain, nausea, vomiting).

Time between the last dose of paracetamol and presentation to hospital

If there were time discrepancies in either the NSWPIC call or medical record screening the worst-case scenario was used i.e. the biggest difference between ingestion and presentation. The hours were rounded to the nearest quarter of an hour.

Time between presentation to hospital and accidental hospital administration of paracetamol

Accidental hospital administration of extra paracetamol was only checked if it was mentioned in any progress notes. The hours (rounded to the nearest quarter) were counted from presentation until the first time it was received.

Time between error given in hospital and phone call to NSWPIC

The hours (rounded to the nearest quarter) were counted from the first error given in hospital until the first call to NSWPIC.

N-acetylcysteine (NAC) administration

For reference, in Australia, for paracetamol poisoning NAC is given as a two-bag infusion with a regimen of 200 mg/kg over 4 h, followed by 100 mg/kg over 16 h [1]. For patients at an increased risk of liver toxicity (determined by high paracetamol concentrations or massive paracetamol overdose) the dose of the second NAC infusion can be increased to 200mg/kg over 16 hours [1] which is often termed 'double dose NAC'. If a patient requires ongoing treatment this is often termed an 'extended regimen' and the NAC infusion is continued at the rate of the second infusion [1].

If the poisons information specialist recommended the use of NAC or if the clinician informed the call taker that it had been given or was intended to be given this was assumed to have been given. If the poisons information specialist deemed that NAC had not already been given and was not required or the clinician was not going to administer it, this was assumed to have not been administered. If the call was taken prior to any results being available (including cases where an individual was referred to hospital) for the poisons information specialist to make a judgement on its use this was left as Unknown.

If NAC was required or given and there was no mention of dose or duration adjustments then the standard regimen was assumed. In the case of increased doses in the second bag this was input as 'double dose NAC'. If the administration was exceeded beyond a normal period specified by the poisons information specialist, this was input as an 'extended regimen'.

Symptoms (detailed analysis)

Symptoms were recorded if they were mentioned at any point of the individual's length of stay or if they were said to occur after the ingestion but prior to presentation. If the individual had vomiting, they were assumed to also have nausea whether or not this was mentioned.

Paracetamol concentrations

Measurement of paracetamol concentrations, in combination with ALT are used to guide the initiation of NAC [1]. Measurements are generally repeated after 8 hours to determine whether the NAC regimen needs to be extended [1]. Time after ingestion was not collected as this is used for measurement against the Rumack-Matthew nomogram which is not validated for RSTIs.

For RSTIs peak paracetamol levels generally occur at the first measurement. As RSTIs are often ingestions of lower doses compared to intentional poisonings this means it is unlikely for there to be any delayed absorption. Treatment with NAC is initiated if the paracetamol concentration is >20 mg/L.

Peak paracetamol level was recorded as the maximum quoted in the call record and was updated if necessary where access to the full medical record was available. For paracetamol quoted as 'above the nomogram' this was recorded as unknown. For paracetamol recorded as < a value this was considered not detected. If levels were given without units specified, mg/L was assumed unless clearly otherwise.

ALT

Measurement of ALT levels, in combination with paracetamol concentrations are used to guide the initiation of NAC [1]. Measurements are generally repeated after 8 hours to determine whether the NAC regimen needs to be extended [1]. ALT levels are also used to diagnose liver toxicity and acute liver injury which is generally defined as ALT > 1000 U/L [1].

For RSTIs patients often have an elevated ALT as symptoms of hepatotoxicity can be delayed. We classified normal ALT as <35 U/L. Treatment with NAC is initiated if the ALT level is >50 U/L.

Peak ALT was recorded as the maximum quoted in the call record and was updated if necessary where access to the full medical record was available. If ALT was quoted as 'normal' this was replaced with the value 34 to allow for analysis (as <35 U/L is considered a normal range for ALT). ALT on presentation was the first recorded ALT level in hospital with the exception of in-hospital errors where the admission ALT was the most recent level before the error.

INR

Measurement of INR is primarily used as an indicator for hepatotoxicity however it is also measured when evaluating patients for cessation of NAC [1].

A normal INR level is 1.0. Amongst other measurements, NAC can be ceased if the INR is <2.0.

Peak INR was recorded as the maximum quoted in the call record and was updated if necessary where access to the full medical record was available. If INR was quoted as 'normal' this was replaced with the value 1.0 to allow for analysis.

Liver unit referral

Liver unit referral was only considered to be caused by paracetamol if specifically mentioned. It was assumed not to occur if it was not mentioned.

Death

Death was only considered to be caused by paracetamol if the ALT at time of death was >1000 U/L.

Length of stay

Length of stay was counted from the presentation/triage time until medical clearance, discharge, death, NAC cessation or recommencement of paracetamol- whichever was the strongest form of clearance from a paracetamol perspective (as the patient may have remained in hospital for reasons other than the paracetamol exposure). In some cases the error with paracetamol was only identified long after presentation however presentation/triage time was still used as the beginning of their length of stay. Length of stay was counted in hours rounded to the nearest quarter of an hour.

Admissions

Admission (yes/no) was recorded, with admissions unrelated to the paracetamol error recorded separately. In hospital dosing errors affecting patients who were already admitted were also recorded separately. If the individual was unable to be officially admitted due to bed constraints but there was an intention to admit by the time of clearance this was still considered an admission.

Additional information on statistical analysis:

Group comparisons based on hospital referrals in Table 2 were conducted using stats R-package. The difference in proportions were tested using the test for equal proportions available in the prop.test() function. For continuous variables we used the wilcox.test() function testing the difference in location parameters between the two-samples (also known as the Mann-Whitney test). The family-wise or simultaneous confidence level of 0.95 was specified. We used the Bonferroni method to estimate the simultaneous 95% confidence interval. Since there were 37 multiple comparisons, individual confidence levels were set to 0.999.

Supplementary Table 1: Background of callers for all calls made to NSWPIC for paracetamol dosing errors, 2017-2023 (N=15597)[a].

Caller Background	n (%)
Community	9764 (62.6)
Hospital doctor	2794 (17.9)
Care worker	1440 (9.2)
Nurse	732 (4.7)
Ambulance	334 (2.1)
General practitioner	318 (2.0)
Other health care professional	137 (0.9)
Other/Unknown	78 (0.5)

Note:
[a] Calls are greater than the number of exposures as one exposure can result in multiple calls from different individuals.
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Supplementary Table 2: Frequency of indications for paracetamol use in community group exposures in 2021 (N=1390).

Indication	**n (%)**[a]
Unknown	666 (47.9%)
Cold/flu symptoms/COVID-19	157 (11.3%)
Migraine/headache	105 (7.5%)
None (wrong patient medicines given)	74 (5.3%)
Dental pain/work	60 (4.3%)
Unspecified pain	60 (4.3%)
Back pain	49 (3.5%)
Post-surgical pain	49 (3.5%)
Joint pain/inflammation	41 (3.0%)
Other	31 (2.2%)
Period pain/menstruation	29 (2.1%)
Ear/nose/throat issues/pain	22 (1.6%)
Post vaccine pain/illness	19 (1.4%)
Bone pain/fracture	15 (1.1%)
Limb pain, other	9 (0.7%)
Fever	9 (0.7%)
Abdominal pain	9 (0.7%)
Nerve pain	9 (0.7%)
Sedation	8 (0.6%)
Neck pain	8 (0.6%)
Anxiety/stress	4 (0.3%)
Flank pain	2 (0.1%)

COVID-19 coronavirus disease 2019

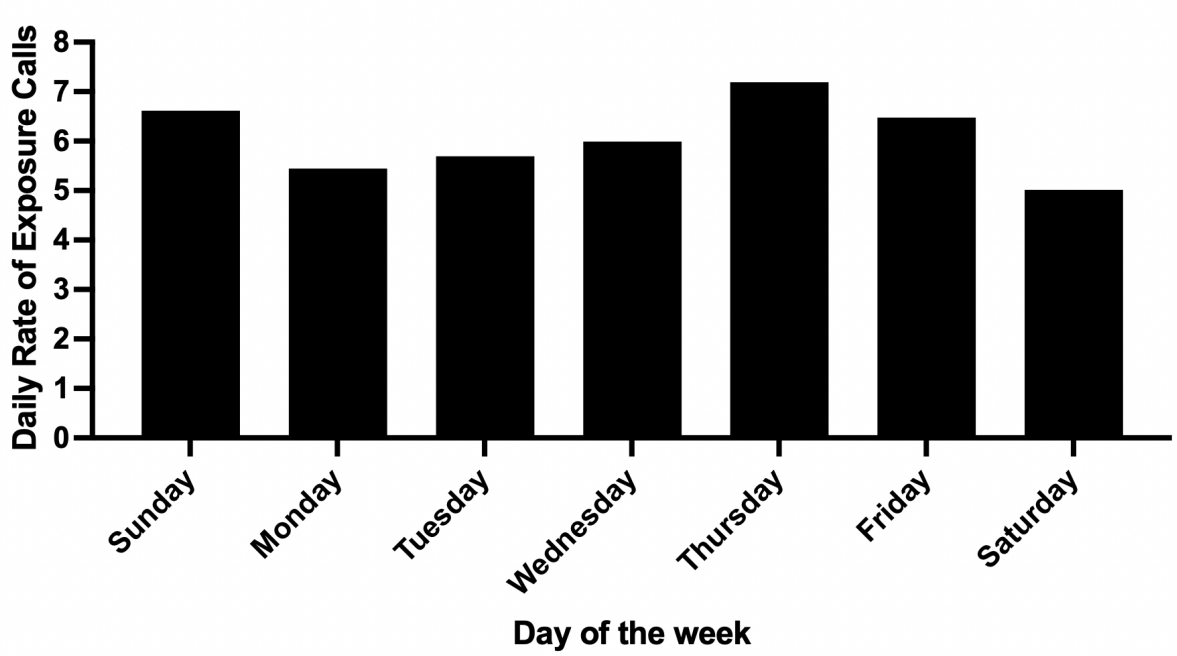
Note:
[a] Adds to >100% as some exposures contain multiple indications.

Supplementary Table 3: Frequency of indications for paracetamol use in hospital group exposures in 2021 (N=509).

Indication	**n (%)**[a]
Dental pain/work	107 (21.0%)
Unknown	86 (16.9%)
Migraine/headache	53 (10.4%)
Unspecified pain	48 (9.4%)
Back pain	35 (6.9%)
Cold/flu symptoms/COVID-19	28 (5.5%)
Other	27 (5.3%)
Abdominal pain	24 (4.7%)
Joint pain/inflammation	20 (3.9%)
Sedation	14 (2.8%)
Ear/nose/throat issues/pain	13 (2.6%)
Period pain/menstruation	12 (2.4%)
Limb pain, other	12 (2.4%)
Neck pain	11 (2.2%)
Post vaccine pain/illness	10 (2.0%)
Bone pain/fracture	9 (1.8%)
Fever	9 (1.8%)
Anxiety/stress	8 (1.6%)
Nerve pain	8 (1.6%)
Post-surgical pain	8 (1.6%)
Flank pain	7 (1.4%)
None (wrong patient medicines given)	1 (0.2%)

COVID-19 coronavirus disease 2019

Note:
[a] Adds to >100% as some exposures contain multiple indications.



Supplementary Figure 1: Weekly pattern of exposure calls to NSWPIC about paracetamol dosing errors, 2017-2023.

Note: Calls were calculated as an average daily rate according to the number of days within this time period**.**
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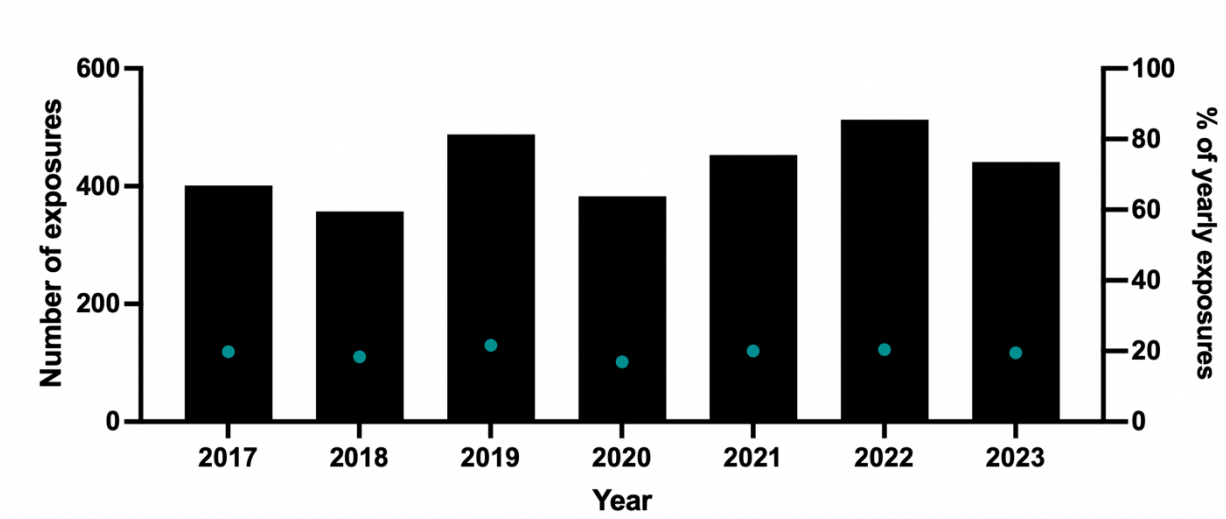

Supplementary Figure 2: Exposures containing multiple paracetamol-containing products per year. Columns represent the number of exposures per year, blue dots represent the percentage of exposures per year.

Note: 2023 count has been doubled to provide an estimated yearly count.

References:

1. Chiew AL, Reith D, Pomerleau A, et al. Updated guidelines for the management of paracetamol poisoning in Australia and New Zealand. Med J Aust. 2020;212:175-183. https://doi.org/10.5694/mja2.50428.
2. Department of Health and Aged Care. Therapeutic Goods (Poisons Standard—February 2024) Instrument 2024. 2024. https://www.legislation.gov.au/F2024L00095/latest/text. Accessed 5 May 2024.