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LETTER TO THE EDITOR

Consumer Healthcare Products Association response to Major *et al*., "Trends in rates of acetaminophen-related adverse events in the United States", *Pharmacoepidemiology & Drug Safety*, May 2016, **25**: 590–8

In the May issue, Major *et al*. examined trends in adverse events associated with use of prescription and over-the-counter (OTC) acetaminophen products (2009–2012) from data within three national surveillance systems reflecting calls to U.S. Poison Centers, emergency department visits, and hospitalizations. The analysis included changes in the number of adverse events over time as well as trends in adverse event rates (per population and per 1 million drug units sold/distributed). The number of adverse events associated with acetaminophen and captured in each of these three databases decreased during the 2009–2012 period. Adverse event rates (per population) also decreased for poison center calls and hospitalizations.

Major *et al*. also estimated the rate of acetaminophen-associated adverse events using sales of acetaminophen-containing products as a proxy for consumer use, to understand how adverse event trends were affected by changes in medicines sold. Despite a reduction in both adverse event numbers and the adverse event rate per population, the authors found an *increase* in event rates (after 2009) when adjusting for changes in sales of acetaminophen (events per million units sold). The authors used IMS Health, National Sales Perspective data as a source of both prescription and OTC acetaminophen drug sales. IMS is an appropriate data source for prescription drug sales, using a scanner-based method that captures over 90% of U.S. pharmaceutical product sales. For OTC products, however, IMS uses a different sample-based method of retail orders from warehouses to project OTC sales to consumers[1] which includes indirect sales of retail and non-retail channels currently collected from 322 wholesalers and 60 drug chain distributors, a panel of over 300 non-federal hospitals, and 142 mail service pharmacies. These "indirect sales" measure the orders to wholesalers and distributors (from retailers) but do not represent a measure of consumer demand/sales. Use of IMS data can lead to a significant gap compared to scanner-based sales data sources with significantly higher sample coverage available from other data providers such as Information Resources Inc. (IRI), with a sample method that captures over 90% of retail sales, and Nielsen.[2]

For perspective, in comparison to the 57% sales decrease estimated by Major *et al*. using the sample-based data projections of IMS, U.S. sales of OTC acetaminophen-containing products (internal analgesic and upper respiratory categories) decreased by 15% between January 2009 and December 2012 according to Nielsen's ScanTrack services. This smaller reduction in U.S. sales of acetaminophen observed with Nielsen scan data was supported by a similar finding observed when IRI scan data were used.[3]

In an analysis completed in 2015 and shared with FDA,[4] Rocky Mountain Poison and Drug Center (RMPDC) analyzed the rate of acetaminophen adverse events using data from the National Poison Data System (2007–2013) similar to what was done by Major *et al*. Similar to the Major *et al*. study, results from the RMPDC analysis demonstrated that the number of acetaminophen exposures reported to U.S. poison centers decreased for both adult single product and multiple product exposures across all exposure reasons (intentional, unintentional, adverse reaction, and other/unknown), as well as within each product type (OTC single ingredient, OTC fixed combination, and prescription fixed combination products) and across all outcomes (minor, moderate, severe effect). In contrast to Major *et al*., the RMPDC analysis demonstrated that the rate of reported adverse events with consideration of the amount of product sold was *decreasing* for each acetaminophen product type. RMPDC calculated that the annual exposure rate per 1 000 000 units sold decreased 3.9% for OTC adult single ingredient acetaminophen products and 8.7% for multi-ingredient

adult acetaminophen products. The multi-ingredient prescription product annual exposure rate decreased 7% over this time period. Thus, using a more accurate source of OTC sales data demonstrates that the rate of acetaminophen adverse events most likely decreased over the observed period, consistent with the results observed over time as well as per population and in contrast to the sales-adjusted results observed by Major *et al*.

The Consumer Healthcare Products Association (CHPA) is committed to enhancing the safe use of all OTC medicines through consumer education efforts and participation in programs implemented to reduce medication errors and unsupervised ingestions, including the Centers for Disease Control and Prevention (CDC) PROTECT Initiative's "Up & Away" education effort and the Acetaminophen Awareness Coalition's "Know Your Dose" campaign. Although continued research-based and targeted interventions are necessary to further reduce acetaminophen exposures, the Major *et al*. study, analyses from the RMPDC[4,5] and recent results from the CDC[6] and Safe Kids Worldwide[7] showing a decline in unsupervised pediatric exposures, provide clear evidence that programs designed to further increase safe acetaminophen use and decrease unsupervised ingestions among young children (a primary driver of the acetaminophen exposures seen in children aged 5 and under, and included in the Major *et al*. analysis) are having a measurable impact.

We agree that continued surveillance and effort are necessary to enhance consumer understanding and further reduce dosing errors across all types of acetaminophen-containing products. The reduction in adverse events associated with all categories of acetaminophen products, including OTC acetaminophen, is a sign that efforts on the part of numerous stakeholders—healthcare providers, patient organizations, manufacturers, and the U.S. Food and Drug Administration—are contributing to better understanding and safer use of acetaminophen.

Denver Health Rocky Mountain Poison and Drug Center performed this analysis and wrote the cited report (National Poison Data System (NPDS) Summary: Acetaminophen Exposures Reported to United States Poison Centers 2007 – 2013). McNeil Consumer Healthcare requested and funded this specific analysis.

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