

The Safety Effects of Child-Resistant Packaging for Oral Prescription Drugs

Two Decades of Experience

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Objective.—To evaluate the effectiveness of child-resistant packaging in reducing the mortality rate for children younger than 5 years from the unintentional ingestion of oral prescription drugs.

Design.—Annual mortality rates for children younger than 5 years associated with the unintentional ingestion of oral prescription drugs are constructed for 1964 through 1992. The effect of child-resistant packaging on the child mortality rate during the postintervention period (1974 through 1992) is evaluated with a multivariate time series regression model. The analysis controls for changes in the consumption of oral prescription drugs over time and for long-term safety trends.

Setting.—United States.

Subjects.—Children younger than 5 years.

Main Outcome Measure.—Estimated reductions in the child mortality rate associated with the use of child-resistant packaging.

Results.—After controlling for covariates, the use of child-resistant packaging was associated with an annual reduction in the oral prescription drug-related mortality rate of 1.40 (95% confidence interval, 0.85-1.95) deaths per million children younger than 5 years. This suggests a reduction of about 460 child deaths from 1974, the year oral prescription drugs became subject to child-resistant packaging requirements, through 1992—a mortality rate reduction of about 45% from levels projected without the child-resistant requirements.

Conclusion.—Child-resistant packaging reduces child mortality from the unintentional ingestion of oral prescription drugs.

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IN 1970, Congress enacted the Poison Prevention Packaging Act (PPPA) to protect children from poisonings resulting from the unintentional ingestion (ie, ingestions not supervised or administered by a parent or guardian) of hazardous household substances.¹ The PPPA authorizes the US Consumer Product Safety Commission (CPSC) to require the use of special child-resistant packaging for toxic substances used in or around the home. Child-resistant packaging is defined by the PPPA to be packaging that is “difficult for children

under age five years to open” but “not difficult for normal adults to use properly.” Current testing protocol requires that at least 80% of children younger than 5 years be unable to open the package within a specified time.²

The special packaging regulations cover 21 categories of household substances, including such diverse products as oral prescription drugs and paint solvents. Oral prescription drugs became subject to child-resistant packaging requirements in 1974. Some preliminary field studies and early postregulatory analyses concluded that child-resistant packaging was effective in reducing medicine-related poisonings of children.³⁻⁷ However, the requirements have provoked some controversy over the years because some adults, especially older adults, have difficulty opening and closing child-resistant packaging.⁸⁻¹⁴ Additionally, a widely publicized 1985 study by Viscusi,¹⁵ which focused primarily on aspirin-related poisonings, challenged

the earlier conclusions: it found no statistical association between child-resistant packaging and the declining child poisoning rate from aspirin products. The author suggested that the earlier studies may have failed to account fully for other factors that contributed to the decrease in child poisonings.

This article describes the results of a time series study designed to assess the effectiveness of child-resistant packaging in reducing the mortality rate of children younger than 5 years from the unintentional ingestion of oral prescription drugs. The study is based on 29 years of annual mortality data, from 1964 through 1992. This represents a substantial expansion of the mortality database when compared with earlier studies and, given that the requirements became effective in 1974, allows us to analyze almost 2 decades of experience with child-resistant packaging. Also, the use of multivariate statistical methods enables us to control for the extraneous and potentially confounding variables that may have affected the child mortality rate independent of child-resistant packaging.

METHOD

Data

Time series data on the deaths of children younger than 5 years are available from the National Center for Health Statistics (NCHS) underlying cause-of-death files for 1964 through 1992.¹⁶ The NCHS data, which are based on records of all deaths occurring in the United States, follow the standardized *International Classification of Diseases (ICD)* manuals of the World Health Organization.

For purposes of this analysis, deaths of children younger than 5 years from the unintentional ingestion of oral prescription drugs are defined as a subset of the deaths reported under the general E-code category “accidental poisoning by drugs, medicaments and biologicals,” currently ICD codes E850 through E858.¹⁷ The subset excludes deaths involving nonpre-

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scription drugs (eg, aspirin and acetaminophen) and deaths involving prescription drugs not covered by the PPPA regulations (eg, topical prescription drugs). E-codes E850-E858 include all deaths resulting from unintentional overdoses but exclude deaths in which the correct drugs were administered properly in therapeutic or prophylactic dosage or deaths in which the drugs were administered with suicidal or homicidal intent.

About 12.8% of deaths included in the analysis were coded by the NCHS as "other" (E858.8) or "unspecified" (E858.9). Deaths coded as other typically resulted from ingestions of multiple drugs classified to different third-digit E-code categories.¹⁸ However, some of these deaths, as well as some of the deaths resulting from the ingestion of an unspecified drug, may have involved drugs not covered by the child-resistant packaging requirements.

The NCHS uses information on the underlying cause of death reported in death certificates to classify the mortality data. Physicians or other qualified persons such as medical examiners or coroners must certify the cause of death.¹⁹ Although the NCHS collected these data continuously for 1964 through 1992, there were some variations in the applicable E-codes based on changes in the World Health Organization's seventh, eighth, and ninth revisions to the *ICD* coding manual (*ICD-7*,²⁰ *ICD-8*,²¹ and *ICD-9*,¹⁷ respectively). Therefore, based on the 3 *ICD* revisions, we looked at the following 3 time periods: 1964 through 1967, 1968 through 1978, and 1979 through 1992. The specific E-codes used to estimate the number of child deaths during each of the 3 reporting periods are as follows: for 1964-1967,²⁰ E870-E878, but excluding E872, E873, and E876; for 1968-1978,²¹ E850-E859, but excluding E852.3, E852.5, E852.7, E853.1, E853.4, E854.3, E856.2, E856.3, E858.0-E858.9, E859.0, and E859.5-E859.8; and for 1979-1992,¹⁷ E850-E858, but excluding E850.1, E850.2, E852.2, E854.1, E855.1, E855.2, and E858.7.

Additional data used in the analysis include annual estimates of the US resident population, including estimates of the number of children younger than 5 years,²² annual estimates of the number of oral prescription drugs dispensed in the United States (B. McClintock, IMS America Ltd, Plymouth Meeting, Pa, written communication, August 1987, and Simonsen²³⁻²⁶) and information on the unintentional injury death rate from all causes for children younger than 5 years.²⁷

Statistical Analysis

Crude mortality rate ratios and differences, including 95% test-based confidence

intervals (CIs), were estimated by comparing child mortality rates (ie, deaths per million person-years) from 1964 through 1973, before child-resistant packages were required for oral prescription drugs, with those from the postregulatory period from 1974 through 1992.

The principal method is a multivariate analysis, using ordinary least-squares regression procedures. The regression model controls for the extraneous and potentially confounding variables that may have affected the child mortality rate independently of child-resistant packaging. The Durbin-Watson statistic was used to test for first-order serial correlation in the error terms. The statistical analysis was performed with MicroTSP, a statistical software package designed for the evaluation of times series data.²⁸ The 2-tailed statistical significance of the regression coefficients is reported at 1% ($P < .01$) and 5% ($P < .05$) significance levels; 95% CIs are also provided for selected coefficients.

The general functional form of the regression model, for the *i*-th year, is given by the following linear equation: Mortality rate = $\beta_0 + \beta_1 \text{prescription}_i + \beta_2 \text{regulation}_i + \beta_3 \text{trend}_i + \beta_4 \text{ICD-7}_i + \beta_5 \text{ICD-8}_i + \epsilon_i$, where β is a vector of coefficients, ϵ_i is a normally distributed error term, and the variables are as follows.

The dependent variable, mortality rate, is the annual child mortality rate resulting from the unintentional ingestion of oral prescription drugs; it is expressed in terms of deaths per million children younger than 5 years.

The variable "prescription" represents the annual per capita consumption of oral prescription drugs and is defined as the annual number of oral drug prescriptions dispensed divided by the US resident population. Annual per capita consumption has been generally rising, from about 4.5 prescriptions per US resident in the mid 1960s to about 6.7 prescriptions in 1992. This variable is included in the model as an aggregate measure of risk exposure and is expected to be directly related to the child mortality rate: the greater the per capita consumption of oral prescription drugs, the greater the likelihood of poisonings associated with those drugs.

The linear trend variable ($\text{trend} = 1$ for 1964, $\text{trend} = 2$ for 1965, . . . $\text{trend} = 29$ for 1992) is included to control for long-term trends in the child death rate that may be independent of child-resistant packaging.

The primary variable of interest is the regulatory variable ("regulation"), which is intended to capture the effect of the requirements for child-resistant packaging on the child mortality rate. Regulation is defined as a dichotomous

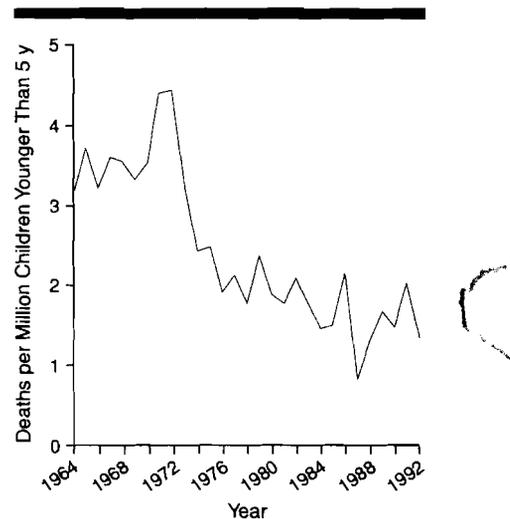


Figure 1.—Child mortality rate due to the unintentional ingestion of oral prescription drugs, 1964-1992.

independent variable such that regulation = 1 for 1974-1992, the years when the child-resistant packaging requirements were applied to oral prescription drugs, and regulation = 0 before 1974.²⁹ The regulatory variable should be inversely related to the child mortality rate if the presence of child-resistant packaging reduces child poisonings.

The regression model also includes 2 categorical variables ("*ICD-7*" and "*ICD-8*") to represent the periods covered by the seventh and eighth revisions to the *ICD*. These variables control for the possible impact of variations in the classification of some child deaths from the 1968 and 1979 *ICD* revisions. The variable *ICD-7* was set equal to 1 for 1964-1967 and equal to 0 otherwise; *ICD-8* was set equal to 1 for 1968-1978, and equal to 0 otherwise. Defined in this way, these variables control for any effects the revisions may have had on the classification of deaths during the earlier periods (1964-1967 and 1968-1978), relative to the later period (1979-1992).²⁹ Since these variables are not substantive, the analysis plan was to exclude them in the second model if their coefficients were not significant at the usual 5% significance level.

Finally, the study describes the results of a sensitivity analysis designed to measure the sensitivity of the statistical results to variations in the specification of the regression model.

RESULTS

Figure 1 shows historical trends in child mortality from the unintentional ingestion of oral prescription drugs from 1964 through 1992. The pattern is quite striking. The mortality rate declined from about 3.5 deaths per million chil-

dren in the late 1960s to less than 2.0 deaths per million children in the early 1990s. Note, however, the somewhat higher mortality rates in 1971 and 1972. The rates for these 2 years may be indicative of a rising mortality rate before the introduction of the child-resistant packaging requirements, possibly linked to increases in the per capita consumption of oral prescription drugs. Alternatively, they may be outliers, in which case the mortality rate could be construed as being relatively constant from 1964 through 1973. In either case, the data display no decrease in the child mortality rate before child-resistant packaging was first required in 1974. They do, however, show a relatively large decrease following the child-resistant packaging requirements.

A reduction in the child mortality rate beginning in 1974 is confirmed by the analysis of the crude mortality rates. Both the crude mortality rate ratio and its difference, which compare the child mortality rate during the preregulatory period (1964-1973) with that of the postregulatory period (1974-1992), show a strong reduction in child mortality following the child-resistant packaging requirements. The mortality rate ratio of 2.01 (95% CI, 1.80-2.24) indicates that the mortality rate during 1964-1973 was about twice that during 1974-1992. Additionally, the mortality rate difference of 1.82 (95% CI, 1.54-2.10) indicates that the mortality rate declined by about 1.82 deaths per million children younger than 5 years after 1973.

This reduction may not, however, be attributable solely to child-resistant packaging. As shown in Figure 2, the unintentional injury death rate for children younger than 5 years from all causes has declined steadily from 1946 through 1992. It decreased from about 600 deaths per million children younger than 5 years in 1946 to about 180 deaths per million in 1992, a reduction of about 70% during the 47-year period.²⁷ This long-term reduction suggests that the decline in the mortality rate associated with the unintentional ingestion of oral prescription drugs may be related in part to long-term safety trends that are independent of child-resistant packaging, including improvements in emergency health care,³⁰ improvements in the delivery of health information through poison control centers and health professionals, and heightened parental awareness of and vigilance against hazards.³¹ These long-term trends must be taken into account in the multivariate analysis.

Regression Results

The Table presents the results of the time series regression analysis. Model 1 includes the shift parameters *ICD-7* and

ICD-8, representing the *ICD* classification periods. However, because the coefficients for these parameters are not statistically significant, they are excluded from model 2.

The coefficients of the trend and prescription variables have the expected signs in both models, although the coefficient for prescription is not significant in model 1 ($P=.13$). More importantly, the coefficient for the regulatory variable is negative and highly significant in both models ($P<.001$), suggesting that the introduction of child-resistant packaging requirements for oral prescription drugs was strongly associated with the reduction in the child mortality rate.

The Durbin-Watson statistic is used to test for first-order serial correlation in the error terms (ie, the correlation between consecutive error terms), a statistical problem that can bias the SEs of the coefficients.²⁹ The Durbin-Watson tests for models 1 and 2 were inconclusive. However, the results of the analysis were not affected when the models were corrected for possible first-order serial correlation.

Since the dependent variable in each regression model was measured in terms of annual deaths per million children younger than 5 years, the negative coefficient for the regulatory variable indicates that the timing of the child-resistant packaging requirements was associated with an annual reduction of about 1.40 (95% CI, 0.85-1.95) deaths per million children younger than 5 years. This is illustrated in Figure 3, which shows the predicted (ie, fitted) estimates of the child mortality rate by year and the predicted mortality rates in the absence of child-resistant packaging. The difference between the 2 mortality rate lines beginning in 1974 represents the estimated reduction in the child mortality rate associated with the use of child-resistant packaging.

Sensitivity Analysis

Several analyses were conducted to evaluate the sensitivity of the statistical findings to variations in the specification of the model. For example, we reestimated the coefficient for the regulation variable under the assumption that the higher child mortality rates associated with the ingestion of oral prescription drugs in 1971 and 1972 were in fact outliers. Under this assumption, we removed the effects of these 2 years by including 2 categorical variables in the regression model, the first set equal to 1 in 1971 and 0 otherwise, and the second set equal to 1 in 1972 and 0 otherwise.³² When these variables were included, the estimated coefficient for the regulation variable was -1.03 (SE, 0.25). Although smaller than the original co-

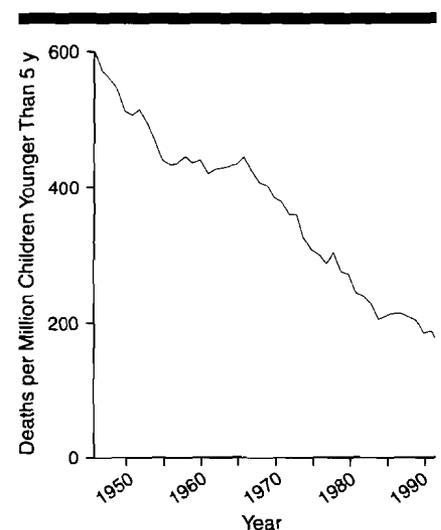


Figure 2.—Unintentional injury death rate for children younger than 5 years from all causes, 1946-1992.

efficient of -1.40 from the Table, it was within the original coefficient's 95% CI (-1.95 to -0.85).

The model was not sensitive either to the specification of the trend variable or to the exclusion of the small proportion of child deaths (12.8%) associated with drugs and other medicaments that were coded by the NCHS as unspecified or other. When the unintentional injury death rate for children younger than 5 years from all causes was substituted for the linear trend variable, the estimated coefficient for the regulation variable was -1.19 (SE, 0.35). Similarly, when the child deaths coded as unspecified or other in the NCHS data were excluded, the estimated coefficient for the regulation variable was -1.27 (SE, 0.24). Again, these coefficients were within the 95% CI of the original coefficient for the regulatory variable.

Finally, a model was specified with terms that were analogous to those used by Viscusi¹⁵ in his regression analysis of aspirin-related poisonings of children younger than 5 years. The Viscusi model included a regulatory variable and an annual per capita aspirin consumption variable similar to the regulation and prescription variables used in the present study. In addition, to account for long-term trends, the Viscusi model included a lagged dependent variable and another variable representing real per capita personal consumption expenditures. When the model was thus specified, the estimated coefficient for the regulation variable was -1.86 (SE, 0.39). Viscusi's formulation of the model suggests an even stronger relationship between child-resistant packaging and the reduction in the child mortality rate.

COMMENT

Child-Resistant Packaging Effectiveness

The results of this time series study provide persuasive and robust evidence of the effectiveness of child-resistant packaging for oral prescription drugs. A statistically significant decrease in the child mortality rate was associated with the introduction of child-resistant packaging, even after controlling for changes in the consumption of oral prescription drugs and for long-term safety trends. Following the 1974 child-resistant packaging requirements, the annual child mortality rate decreased by an estimated 1.40 deaths per million children younger than 5 years.

This reduction is substantial as well as statistically significant: it equates to about 460 fewer child deaths from 1974 through 1992. This averages to about 24 fewer child deaths annually, a reduction of about 45% from levels that were projected in the absence of child-resistant requirements. Moreover, the results were not sensitive to reasonable variations in the specification of the regression model.

To the extent that child-resistant packaging also prevents nonfatal ingestions, which constitute the great bulk of the unintentional child ingestions of oral prescription drugs, the results underestimate the benefits of child-resistant packaging. According to the CPSC's National Electronic Injury Surveillance System, there were an estimated 27 500 (95% CI, 21 000 to 34 000) nonfatal child ingestions involving oral prescription drugs treated in hospital emergency departments in 1989.^{33,34} Unfortunately, no suitable preregulatory data on nonfatal poisonings are available for comparison with postregulatory data. The National Clearinghouse for Poison Control Centers at the US Food and Drug Administration collected exposure data on nonfatal child poisonings from 1957 through 1983. However, these data were unsuitable for deriving population-based poisoning rates or secular trends of those rates. Participating poison control centers joined and left the program periodically, many reported only sporadically, and the size of the population being served by participating poison control centers varied but was never measured (M. Fow, PhD, Food and Drug Administration, Bethesda, Md, written communication, April 1987).

The results of the present analysis differ from those of the Viscusi¹⁵ study, which did not find a statistical association between child-resistant packaging and either the nonfatal or fatal aspirin poisoning rate for children. With respect to nonfatal ingestions, this may be because the Viscusi study relied on the poison control center data just described.

Regression Results for Predicting the Mortality Rate From the Unintentional Ingestion of Oral Prescription Drugs for Children Younger Than 5 Years

Variables	Model 1*			Model 2*		
	Coefficient	SE	P	Coefficient	SE	P
Intercept	1.90	1.40	.19	1.72†	0.81	.04
Prescription	0.40	0.25	.13	0.37†	0.14	.01
Trend	-0.06†	0.03	.04	-0.05‡	0.02	.006
Regulation	-1.40‡	0.27	<.001	-1.39‡	0.26	<.001
ICD-7§	-0.35	0.48	.47
ICD-8§	-0.25	0.36	.51

*For both models, $R^2=0.87$; Durbin-Watson=2.38.
 † $P<.05$, 2-tailed test.
 ‡ $P<.01$, 2-tailed test.
 §ICD indicates *International Classification of Diseases*. These covariates were not included in model 2 because their coefficients were not statistically significant.

Additionally, the Viscusi¹⁵ analysis of the mortality data may not have adequately controlled for factors other than child-resistant packaging. For example, the analysis did not control for the rapid reduction in the aspirin-related mortality rate that occurred before child-resistant packaging requirements became effective in 1972. The mortality rate decreased dramatically from about 6.2 child deaths per million children younger than 5 years in 1964 to about 2.6 deaths per million children in 1971—a reduction of almost 60% in the 7 years before child-resistant packaging was required. This decrease, which confounded the relationship between the aspirin-related child mortality rate and child-resistant packaging, was probably related to efforts designed to reduce the incidence of unintentional poisonings from overdoses of aspirin administered by parents or guardians,^{3,35,36} poisonings that child-resistant packaging would not have been expected to prevent in any event. The relationship between child-resistant packaging and the aspirin-related child mortality rate may also have been confounded by the fact that 2 major manufacturers of children's aspirin voluntarily adopted the use of child-resistant packages in 1969 and by the voluntary introduction of child-resistant packaging on some adult aspirin products as early as 1971, well before the child-resistant packaging requirements became effective.³

The present study did not suffer from the severe confounding difficulties in the aspirin-related mortality data. There is no evidence that oral prescription drugs mistakenly administered by parents or guardians in doses higher than those recommended by physicians constituted a widespread problem at any time during the study period. Nor was there substantial use of child-resistant packaging with oral prescription drugs before the requirements went into effect.

Nevertheless, the estimated 45% reduction in the child mortality rate from the unintended ingestion of oral prescription drugs is less than might be expected given that the current testing

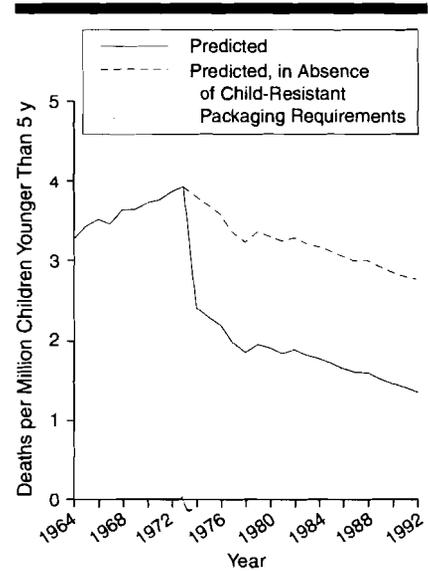


Figure 3.—Fitted model for predicted child mortality rate due to the unintentional ingestion of oral prescription drugs, 1964-1992.

protocol for child-resistant packaging requires that at least 80% of children be unable to open child-resistant packages during a specified test period.² In other words, the reduction is less than might have been expected based solely on the technological aspects and testing experience of child-resistant packaging.

There are, however, at least 2 observable factors that can help explain the lower 45% reduction in the child mortality rate. First, a large percentage of the unintentional poisonings of children younger than 5 years (perhaps as many as 40%, according to a 1989 CPSC study of nonfatal poisonings resulting in hospital emergency department medical treatment³³) involve drugs that are dispensed in conventional, non-child-resistant packaging. Non-child-resistant packaging is available under the PPPA because Congress wanted to ensure that substances subject to child-resistant requirements are "readily available to elderly or handicapped persons unable to use such substances when pack-

aged in [child-resistant packaging].³⁷ As a result, prescription drugs can be dispensed in non-child-resistant packaging if directed by the prescriber or if requested by the purchaser.^{2,10} There is also evidence of noncompliance with the child-resistant requirements by some pharmacists.^{36,39}

Second, a substantial proportion of child poisonings involved medicines originally dispensed in child-resistant packages that were left unsecured (ie, not in a child-resistant mode) at the time of ingestion.^{33,40}

Overall, more than 50% of all oral prescription drug-related poisonings of children younger than 5 years may involve medicines either originally dispensed in conventional non-child-resistant packages or in child-resistant packaging that has been disabled. It is also worth noting that a large proportion of prescription drug poisonings, perhaps as many as 20% to 25%, occur outside the child's home,^{33,40} and many involve the medications of grandparents and other older persons.³³

Recent Efforts to Improve Child-Resistant Packaging

These findings suggest that further reductions in the child poisoning rate

are possible if more consumers, including older consumers, use child-resistant packaging and use it correctly.

The CPSC has recently acted to increase consumer acceptance of child-resistant packaging by encouraging packaging designs that are both child-resistant and easier for all adults to open and close. Specifically, the agency revised the testing protocol for child-resistant packaging to promote designs that are easier for older persons to open but do not compromise the child-resistant characteristics of current child-resistant packaging.⁴¹

The revised test protocol applies to products packaged on or after January 21, 1998. It includes a child test to make sure that a large majority of young children are unable to open child-resistant packaging and an adult test to make sure that adults can properly use the packages. The major change is the substitution of 100 older adults, aged 50 to 70 years, for the current adult panel, aged 18 to 45 years. In order for a child-resistant package to pass the revised adult test, at least 90% of the test subjects must be able to open the package twice within allotted test periods. The child test will still require that at least

80% of children are unable to open child-resistant packages during the specified test period.

Child-resistant packaging that passes the new protocol should ultimately lead to reduced child poisonings by increasing the use of more user-friendly child-resistant packaging. The public health community can help achieve this by encouraging all consumers, even older people with limited exposure to young children, to use child-resistant packaging.

Consumers of all ages should also always be encouraged to keep medicines out of the reach of children, even when they are in child-resistant packaging. The fact that many child poisonings involve medicines that are in child-resistant packaging at the time of ingestion shows that child-resistant packaging is not childproof. Therefore, parents and caregivers (and other adults who have child visitors) must be reminded that child-resistant packaging is no substitute for the safe storage of medicines or for close adult supervision.

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