

U. S. Food and Drug Administration
Center for Food Safety and Applied Nutrition
Office of Plant and Dairy Foods and Beverages
June 15, 2000

Patulin in Apple Juice, Apple Juice Concentrates and Apple Juice Products

(Draft) Guidance for FDA Components and Industry:
Apple Juice, Apple Juice Concentrates, and Apple Juice Products
- Adulteration with Patulin

Table of Contents

- I. Introduction
- II. Safety Assessment and Risk Management for Patulin
 - 1. Synopsis
 - 2. Reviews of Toxicity Data; NOAEL
 - 3. Provisional Tolerable Daily Intake
 - 4. Assessment of exposure to patulin versus PTDI
 - A. Initial assessment
 - B. Revised assessment
 - 5. Action Level
- III. Additional Considerations
 - 1. Review by FDA's Food Advisory Committee
- IV. Conclusion

References

I. Introduction

Patulin is a mycotoxin that is produced by certain species of *Penicillium*, *Aspergillus*, and *Byssochytrium* molds that may grow on a variety of foods including fruit, grains and cheese. Patulin has been found to occur in a number of foods including apple juice, apples and pears with brown rot (Harwig et al. 1973, Brain et al. 1956), flour (Hasseltine and Graves, 1966), and malt feed (Ukai et al. 1954). However, given the nature of the food, the manufacturing processes, or consumption practices for many foods, patulin does not appear to pose a safety concern, with the exception of apple juice (Fritz, 1981). For instance, the rotten portions of most fruits and grains are typically removed prior to consumption. In foods such as cheese, the high cysteine content of the food interacts with patulin to render it inactive (Ciegler et al., 1977). Patulin is reported to be destroyed by fermentation and thus is not found in either alcoholic fruit beverages or vinegars produced from fruit juices. Thermal processing appears to cause only moderate reductions in patulin levels, thus patulin present in apple juice will survive the pasteurization processes (IARC 1986, WHO 1990, Harrison 1989, McKinley and Carlton, 1991).

Patulin has been found to occur at high levels in some apple juice products offered for sale or import in the U.S. FDA is currently soliciting public comment on a draft Compliance Policy Guide (CPG) that describes FDA's internal enforcement guidance concerning patulin in apple juice products.

In this supporting document, FDA presents the scientific information and the risk management considerations it took into account in arriving at the 50 µg/kg action level which is part of the draft CPG.

II. Safety Assessment and Risk Management for Patulin

1. Synopsis

FDA employed the "safety assessment" method as the risk assessment approach for considering the available safety data on patulin. The outcome of the safety assessment was used by FDA to evaluate whether processors may need to implement controls for patulin in apple juice, and to identify a level, (i.e., an "action level") at which FDA would consider taking legal action against apple juice products bearing patulin under Section 402(a)(1) of the Federal Food Drug and Cosmetic Act, which states that a food is "adulterated" if it bears or contains an added poisonous or deleterious substance which may render it injurious to health.

The safety assessment method, originally described in a 1954 paper by Lehman and Fitzhugh (Lehman and Fitzhugh, 1954), introduced the use of 10-fold safety factors, which later also became known as "uncertainty factors," in assessing the safety of substances, e.g. contaminants, in food. Lehman and Fitzhugh described the application of the 10-fold safety/uncertainty factors as useful for establishing a "target" margin of safety. However, they concluded there were no scientific or mathematical means by which absolute values for these factors could be derived. Over the years these factors have been routinely used both in the U.S. and internationally to ensure an adequate margin of safety (WHO, 1987).

Typically, for a contaminant in a food such as apple juice, where there is a potential for chronic exposure to the contaminant, FDA would determine the exposure level that would ensure an adequate safety margin by applying two 10-fold safety factors (equating to a 100-fold safety factor) to the "no observed adverse effect level" (NOAEL) from lifetime animal feeding studies. One safety factor accounts for the extrapolation from animal data to humans (i.e., interspecies variation), and the second accounts for variation in sensitivity to the contaminant's effects within humans (i.e., intraspecies variation). This calculation yields a provisional tolerable daily intake (PTDI) or provisional tolerable weekly intake (PTWI) for the contaminant.

The margin of safety for eaters is determined by estimating the daily or weekly exposure to the contaminant (using food consumption data and occurrence data for the contaminant in food) for a representative segment of eaters, and comparing that estimated exposure to the PTDI or PTWI.

An action level may be identified by calculating a maximum level for the contaminant in the food that would ensure that exposure to the contaminant results in an acceptable margin of safety, considering the PTDI or PTWI.

In deriving the proposed action level for patulin, FDA considered consumption of apple juice by drinkers of all ages and by small children in two age categories, children less than one year old and children 1-2 years old. The two age categories for small children were considered because small children consume higher amounts of apple juice relative to their body weight than other age groups.

2. Reviews of Toxicity Data; NOAEL

Patulin toxicity data are reviewed in detail in: "IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans" (IARC, 1986) and "Toxicological evaluation of certain food additives and contaminants" (WHO, 1990). In addition to considering these reviews,

FDA independently reviewed the available information on patulin toxicity (FDA Memorandum, 1994).

FDA's review found that the toxicological studies on patulin demonstrate that patulin is toxic upon repeated administration of oral doses around 1.5 mg/kg body weight (bw), which caused premature death in rats (Becci et al., 1981). Studies have not demonstrated convincing evidence of carcinogenicity or of germ cell mutagenic potential. The studies demonstrate that fetotoxic or embryotoxic effects in rodents occurred only after administration of patulin doses that were also overtly toxic to the mothers. The studies demonstrate that immunotoxic effects are associated only with patulin doses that are much higher than those to which humans are exposed (Llewellyn et al., 1998).

The NOAEL for patulin was derived from a 109 week feeding study (Becci, et al. (1981)) in which doses of 0.0, 0.1, 0.5, and 1.5 mg/kg bw, were administered to both male and female rats three days per week by gastric intubation. Patulin at the high dose level caused a significant increase, compared to controls, in the mortality rate in both sexes. These effects could have resulted from the mechanics of repeated intubation.

No adverse effects were observed in the group receiving the lowest dose level, i.e., 0.1 mg/kg bw three times per week. That group received a cumulative weekly dose of 0.3 mg/kg bw, which is the NOAEL FDA used in its safety assessment.

Generally, animal studies are considered by safety experts to be appropriate models for assessing potential adverse effects in humans. However, animal studies that demonstrate adverse effects would not be used in assessing potential human health effects if it was established by mechanistic or other studies, that the toxic effects observed in animals would not occur in humans. FDA is not aware of any mechanistic or other data that would suggest that the effects observed in the study of Becci, et al. will not occur in humans at some level of exposure to patulin. Therefore, based upon adverse effects due to patulin in animal studies, FDA believes that humans may be at risk of harm at some level of exposure to patulin.

3. Provisional Tolerable Daily Intake

After its own independent evaluation of the data, FDA concurs with the PTDI for patulin, which was established at the 44th meeting of the Joint Expert Committee on Food Additives (JECFA) in 1995. JECFA is an international organization that provides science based toxicological evaluations of food additives and contaminants and advises the Codex Committee on Food Additives and Chemical Contaminants on risk assessment of substances of interest to that committee. JECFA had originally established a PTWI for patulin at its 35th meeting in 1990. JECFA subsequently took into account the fact that most of the patulin ingested by rats is eliminated within 48 hours. The absence of accumulation ultimately led JECFA to establish a maximum provisional tolerable daily intake (PTDI) of 0.43 µg /kg bw per day. The PTDI is derived from the NOAEL for patulin from the Becci study, i.e. 0.3 mg/kg bw per week. That weekly intake is converted to a daily intake by dividing it by 7, and that result is divided by 100 to apply the two 10-fold safety factors to arrive at the PTDI, as follows:

1. 0.3 mg/kg bw per week divided by 7 = 0.043 mg/kg bw per day
2. 0.043 mg/kg bw per day divided by 100 (safety factor) = 0.00043 mg/kg bw per day, or 0.43 µg/kg bw per day, which is the PTDI.

4. Assessment of exposure to patulin versus PTDI

Two exposure assessments were calculated, FDA's initial assessment and a revised assessment that was carried out after FDA's Food Advisory Committee reviewed the scientific information supporting an action level for patulin, as discussed below.

In evaluating the estimated exposure to patulin with respect to the PTDI, FDA considered the estimated exposure to patulin for drinkers of "all ages" and for small children in two age categories, children less than one year old, and children 1-2 years old. The interpretation of the exposure estimates for the various age categories with respect to the PTDI is discussed below in section 4 B., "Revised assessment."

To estimate exposure to a dietary contaminant FDA must obtain intake (consumption) data for the food bearing the contaminant, and data on the occurrence level for the contaminant in that food. If age specific intake data are available, exposure may be calculated for specific age groups, as was done in this instance.

In making both sets of estimates, the FDA used a probabilistic modeling method known as a "Monte Carlo analysis" to estimate patulin exposure (Rubinstein, 1981). Monte Carlo simulations can be used to evaluate models in which one or more inputs (in this case, food intakes and patulin levels) can be defined by a distribution of values. A Monte Carlo simulation takes a random value from the distribution of possible values for the input, uses that value in calculating the outcome of the model, stores the result, and then repeats the procedure a determined number of times (iterations) using new random values of the input taken from the distribution for each iteration. The resulting output from this procedure (e.g., exposures) is a range of possible outcomes for the model. A probability distribution function can be prepared from the range and can be used to estimate exposures (typically mean and/or 90th percentile) to substances in the diet. It should be stressed, however, that the model FDA used assumes that food choices are random, which might not be appropriate for a "visible" additive, such as a high-intensity sweetener.

The availability of distributions of food intakes, patulin levels in apple juice and apple juice containing products, and survey information evaluating the percentage of eaters of each food in the population, as well as the invisibility of patulin in food, enable the use of Monte Carlo modeling for evaluating patulin exposure.

The juice intake data used to calculate exposure were taken from the 1994-1996 United States Department of Agriculture Nationwide Food Consumption Survey (category: Apple Juice Specified as an Ingredient). This category encompasses apple juice intake as pure juice, as well as an ingredient in juice blends and other foods. The food consumption data are based on 2 day food consumption surveys of consumers, which are very short survey times that result in overestimation of actual long-term consumption. Long-term food consumption surveys would be most appropriate to use considering that the PTDI was based upon a lifetime animal bioassay. However, since long-term consumption data are seldom available, the 90th percentile exposure from short term food consumption surveys are usually used, and this approach is considered by experts to be a conservative approach that ensures that an appropriate degree of protection is obtained in the safety assessment.

A. Initial assessment

Patulin occurrence data were taken from 2977 samples of apple juice analyzed for patulin levels. The majority of the samples were commercial samples taken from lots of bulk juice and analyzed privately for the industry, and the results were made available to FDA. Such analyses are typically performed by industry to determine the acceptability of a lot of juice

offered by the supplier. The remaining samples were collected and analyzed by FDA as part of its monitoring and enforcement activities.

The patulin level inputs were taken from patulin occurrence data in apple juice that were categorized into groups with ranges of <5, 5-49, 50-99, 100-199, 200-500, and >500 µg/kg. For each iteration during the Monte Carlo analysis, a patulin group was first selected from one of these groups based on the frequency of samples in each group. After a group was selected, a patulin value was then calculated by the computer based upon the assumption that the patulin values would be uniformly distributed about the mid-value of each range. This approach was used because at the time FDA conducted the initial assessment it did not have the actual measured patulin levels for many of the apple juice samples tested for industry. Rather, much of the industry data was originally reported to FDA as categorized data, i.e. the number of samples with patulin levels within the above ranges.

The estimated exposures to patulin are presented in Tables 1 and 2 (Apple juice intakes are expressed as grams per person per day; Patulin exposures are expressed as µg/kg bw per day; Mean body weights used in the calculations are 8 kg for <1 year olds, 12 kg for 1-2 year olds, and 64 kg for the all ages group (Johnson, 1974)).

The estimated patulin exposures shown in Table 1 were calculated using patulin levels from all 2977 apple juice samples. Industry sources have informed FDA that the samples analyzed by industry include many commercial lots that were rejected by the importers for excessive patulin. Thus, the estimated patulin exposures presented in Table 1 likely exaggerate actual patulin exposures and reflect upper bound potential exposures if processors exercise no controls for patulin. In Table 2, the 545 samples with a patulin level greater than 50 µg /kg were excluded from the Monte Carlo simulation to represent the expected impact on exposure of processors implementing controls for patulin to limit its occurrence in accord with the level set out in the guidance.

Table 1 No Juice Samples Excluded				
Age Group	Mean Apple Juice Intake (g/p/d)	Mean Patulin Exposure (µg/kg bw/d)	90th Percentile Apple Juice Intake (g/p/d)	90th Percentile Patulin Exposure (µg/kg bw/d)
All ages	200	0.094	250	0.22
1 -2 years	216	0.58	434	1.3
<1 year	128	0.50	372	1.1

Table 2 Juice Samples with Patulin Levels > 50 µg /kg Excluded				
Age Group	Mean Apple Juice Intake (g/p/d)	Mean Patulin Exposure (µg/kg bw/d)	90th Percentile Apple Juice Intake (g/p/d)	90th Percentile Patulin Exposure (µg/kg bw/d)
All ages	200	0.031	250	0.078
1 -2 years	216	0.17	434	0.42
<1 year	128	0.13	372	0.38

The results in Table 1 indicate that if processors do not implement controls for patulin, the estimated 90th percentile patulin exposure for apple juice drinkers of all ages would be below the PTDI of 0.43 µg /kg bw per day. However, the exposure for children under 1 year of age would be nearly 3 times the PTDI and exposure for children 1-2 years old would be 3 times the PTDI (equating to only a 33-fold margin of safety compared to the NOAEL).

The results in Table 2 indicate that if processors implement controls for patulin at the 50 µg/kg level, the estimated 90th percentile patulin exposure for all the age groups considered would not exceed the PTDI of 0.43 µg /kg bw per day. In fact, the exposure for apple juice drinkers of all ages, would be 5-fold less than the PTDI, providing a 500 fold safety factor (considering the PTDI incorporates a 100-fold safety factor) for lifetime consumption. Exposure would be slightly below the PTDI for children under 1 year of age, and essentially at the PTDI for 1-2 year old children, meaning that at least a 100-fold safety factor would exist for children in these age categories under this assessment.

B. Revised assessment

FDA presented the above scientific information supporting the establishment of an action level for patulin to its Food Advisory Committee (FAC) in June 1999 (see discussion below). In response to comments made by some members of the FAC, FDA subsequently carried out a revised assessment of exposure to patulin to ensure the best possible assessment of exposure to patulin.

FDA subsequently obtained the measured patulin levels for 2647 apple juice samples, including many of the 2977 samples considered in the initial assessment and also some more recently analyzed samples. In addition, industry provided the patulin results for 118 samples of apple juice intended for infants. In the revised assessment, the Monte Carlo calculations were based upon the actual values for patulin in the 2647 samples for the "all ages" group and the 1-2 year old group. For each iteration, an actual patulin value was selected from the sample population. For the <1 year old group, detailed analysis of available intake data, determined that 71% of the time these infants receive apple juice intended for infants. Therefore, for this group, the simulation selected a sample from juice intended for infants 71% of the time and from the large sample population the remainder of the time. The results from the revised assessment are presented in Tables 3 and 4.

Table 3 No Juice Samples Excluded				
Age Group	Mean Apple Juice Intake (g/p/d)	Mean Patulin Exposure (µg/kg bw/d)	90th Percentile Apple Juice Intake (g/p/d)	90th Percentile Patulin Exposure (µg/kg bw/d)
All ages	200	0.14	250	0.26
1 -2 years	216	0.80	434	1.7
<1 year	128	0.21	372	.40

Table 4 Juice Samples with Patulin Levels > 50 µg /kg Excluded				
Age Group	Mean Apple Juice Intake (g/p/d)	Mean Patulin Exposure (µg/kg bw/d)	90th Percentile Apple Juice Intake (g/p/d)	90th Percentile Patulin Exposure (µg/kg bw/d)
All ages	200	0.04	250	0.10
1 -2 years	216	0.22	434	0.67
<1 year	128	0.13	372	0.27

The results of the revised assessment in Table 3 indicate that if no controls for patulin levels are carried out by processors, the estimated 90th percentile patulin exposure for apple juice drinkers of all ages would be approximately one half of the PTDI of 0.43 µg /kg bw per day. However, the exposure for children under 1 year of age is approximately the same as PTDI and exposure for children 1-2 years is 4 times the PTDI (equating to only a 25-fold margin of safety compared to the NOAEL).

The results of the revised assessment in Table 4 indicate that if processors implement controls for patulin at the 50 µg/kg level, the estimated 90th percentile patulin exposure for drinkers of all ages would be 4-fold less than the PTDI, providing a 400 fold safety factor for lifetime consumption. The estimated exposure for the <1 year old age group would be approximately one-half of the PTDI. The estimated exposure for 1-2 year old children

would be slightly above the PTDI; however, a 64-fold margin of safety in comparison to the NOAEL would still exist for this group.

In carrying out a safety assessment, FDA generally considers only the estimated exposure for "all ages" when the PTDI has been derived from a lifetime feeding study, as is the case for patulin. In such a case, FDA would consider that there is an adequate margin of safety if the estimated patulin exposure for the 90th percentile apple juice drinker of "all ages" is less than or equal to the PTDI. In the lifetime feeding study, the animals in each dosage group were exposed to a single patulin dose level (relative to body weight) throughout their lives. In contrast, FDA recognizes that human exposure to patulin varies substantially according to age. Patulin exposure in small children is higher relative to body weight because small children consume significantly greater amounts of apple juice relative to their body weight. Thus, FDA also considered the estimated exposure to patulin by children in these two age categories with respect to the PTDI.

FDA believes that in view of the greater exposure to patulin by small children, the exposure for drinkers of all ages should be significantly below the PTDI to ensure an adequate margin of safety for long term consumption of apple juice. If long term exposure to patulin is significantly below the PTDI, FDA believes that it is not necessary for patulin exposure for small children to be at or below the PTDI during this relatively short portion of the lifespan. However, during this portion of the lifespan, e.g., ages 1-2, the estimated exposure for 90th percentile drinkers should still provide for a substantial margin of safety with respect to the NOAEL.

In this manner, Table 4 indicates that public health protection will be achieved if processors control patulin levels in apple juice to not exceed the action level. Estimated exposure for drinkers of all ages is significantly below the PTDI (i.e., there is a 400 fold margin of safety for lifetime consumption) and a 64-fold margin of safety exists for 1-2 year old children.

Conversely, if processors do not control patulin levels in apple juice, the exposure estimates in Table 3 indicate that for children 1-2 years old, the margin of safety with respect to the NOAEL would be only 25-fold. FDA believes that this relatively low margin of safety and the accompanying greater long-term exposure may not provide optimum long-term protection for consumers.

Furthermore, the exposure estimate in Table 4 likely overestimates the exposure to patulin that will occur if processors of apple juice implement controls for patulin. This is because FDA expects that, in order to have a high degree of confidence that their products will not exceed the action level, juice manufacturers will exercise the necessary degree of control (e.g. strict quality specifications on incoming apples), to ensure that their products are actually well below the action level. This appears to have occurred in the United Kingdom (U.K.). In 1993, the U.K. Ministry of Agriculture, Food, and Fisheries (MAFF) set a patulin advisory level of 50 µg /kg in apple juice. Since that time, the percentage of apple juice samples in the U.K. containing patulin levels above the advisory level has been reduced and patulin levels have also been reduced in samples that comply with the advisory level. Prior to the implementation of the advisory level, 27% of samples in the U.K. had less than 10 µg /kg patulin and 7% of the samples contained 10-24 µg /kg. The 300 samples analyzed in Britain in 1998 had 69% and 22%, respectively, in those two categories (MAFF, 1999).

A similar change in the distribution of patulin levels in apple juice samples in the U.S. would change the exposure estimates presented in Table 4. When, for example, the 300

patulin samples from the 1998 British survey were used to calculate the exposure of the 90th percentile U.S. apple juice drinker for the age groups "<1 year", "1-2 years", and "all ages", the exposure values were 0.34, 0.40, and 0.06 µg/kg bw per day respectively. The exposures for children <1 year of age and children 1-2 years old would be essentially at the PTDI. This further supports that a 50 µg/kg action level would provide an adequate margin of safety for consumers.

In addition, the exposure estimates in Table 4 may overestimate exposure to patulin for children who often consume apple juice that has been diluted with water. In fact, the American Academy of Pediatrics advises parents who frequently offer juice to their children to dilute the juice, ½ portion of juice to ½ portion of water (Dietz and Stern, 1999). FDA has not attempted to quantify any additional margin of safety that would be realized for children who consume diluted apple juice because not all parents may dilute the juice they serve to their children and an adequate margin of safety exists without accounting for the practice of dilution.

5. Action Level

Based upon the above discussion FDA believes that if processors do not implement controls for patulin, consumers may not be optimally protected from potential adverse effects due to long-term exposure to patulin from the consumption of apple juice. FDA thus believes that it is appropriate that apple juice processors voluntarily establish controls for patulin. Based upon the exposure estimates in Table 4, FDA believes that drinkers of apple juice would be at negligible risk of adverse health effects from patulin if patulin levels in apple juice were controlled by processors to a level of 50 µg/kg or below.

Control of patulin levels in apple juice is achievable in practice. Most frequent patulin contamination results from contamination with mold on apples with surface damage. For example, in a study, Lovett et al. (1975) purposefully contaminated apples in a controlled manner with patulin-producing mold. The investigators then successfully reduced patulin contamination approximately 90% by trimming away the rotten portion of the fruit. FDA believes that control by processors of patulin levels to 50 µg/kg or below can be achieved principally by removing spoiled and visually damaged apples from the product stream used for the production of apple juice.

Other measures such as water treatment may also be effective in reducing patulin levels. Sydenham et al. (1995) found a significant reduction of patulin levels following an initial water treatment step and following removal by hand of rotten and damaged fruit prior to juice production.

Evidence also suggests that certain varieties of apples with an open calyx (blossom end) are particularly susceptible to patulin formation within the core of the apple. In such a situation, damage to the fruit it is not easily observed and the apple may not be removed from juice production (British Code of Practice, 1993). Therefore, the presence of patulin in juice made from seemingly wholesome fruit cannot be totally avoided.

III. Additional Considerations

1. Review by FDA's Food Advisory Committee

FDA presented the scientific information supporting an action level of 50 µg/kg for patulin in apple juice and apple juice containing products to its Food Advisory Committee (FAC) in June of 1999. The presentation to the FAC was based upon the "Initial assessment" presented above.

The FAC supported FDA's recommendation that an action level be set for patulin in apple juice and apple juice containing products. It further agreed with FDA's analysis that a patulin level of 50 µg/kg of apple juice on a ready-to-eat basis would be sufficient for protection of human health. Some FDA members qualified their agreement with the level of 50 µg/kg by expressing a desire for more information in three areas. The FDA has researched these areas as requested and the results are discussed below.

Some members of the FAC asked whether more current information about apple juice consumption by young children was available. The agency looked for more current information about apple juice consumption for the two age groups considered, but was unable to locate any more recent or reliable information. The data from the 1994-1996 United States Department of Agriculture Nationwide Food Consumption Survey are the best consumption data available, and FDA is not aware of any reason why these data are not suitable for use in the safety assessment for patulin. However, in response to the comments of these members of the FAC that stressed the need to ensure adequate protection for small children, FDA carried out the "Revised assessment" of exposure to patulin described above.

Commenting on the data in one of the tables presented in the Becci study, a member of the FAC also questioned whether FDA in its safety assessment, had properly incorporated the doses of patulin received by the rats in the study. FDA subsequently checked with one of the authors of the study who stated that the doses of patulin presented in the published paper, e.g., 0.0, 0.1, 0.5, and 1.5 mg/kg bw, were the doses given by gavage three times per week. FDA did properly incorporate the doses received by the rats in its safety assessment, as did JECFA when calculating the PTDI.

A member of the FAC expressed concern that the elderly in institutional settings (e.g., nursing homes) may consume high amounts of apple juice. The agency did not evaluate intake by the elderly as a separate class. Instead, their intake was considered in the "all ages" category. In response to the committee member's comment, the agency did review the information it had available on the intake of apple juice by the elderly. Although data on intake by the elderly in institutional settings were not available, intake by the elderly among the general population was not significantly different than intake for the all ages group. Given the 400-fold margin of safety for drinkers in the all ages group, if in fact, the elderly in institutional settings consume significantly more apple juice than the elderly in the general population, FDA believes that a substantial margin of safety would still exist for the elderly in institutional settings.

IV. Conclusion

The information presented in this paper supports a 50 µg/kg action level for patulin in apple juice, apple juice concentrates, and apple juice products based on the level found or calculated to be found in single strength apple juice or in the single strength apple juice component of the product.

References

- Becci, P. J., Hess, F. G., Johnson, W. D., Gallo, M. A., Babish, J. G., Dailey, R. E., & Parent, R. A. (1981) Long-term carcinogenicity and toxicity studies of patulin in the rat. *J. Appl. Toxicol.* 1(5):256-261.
- Brain, P. W. (1956) Production of patulin in apple fruits by *Penicillium expansum*, *Nature (London)* 178: 263.
- British Code of Practice for the Production of Apple Juice, British Soft Drinks Association, November 1993.
- Ciegler, A. (1977) Patulin. Rodricks JV et al. (ed) *Mycotoxins in human and animal health*. Pathotox Publ. p 609-623.
- Dietz, W.H. and Stern, L. (ed) (1999) *American Academy of Pediatrics, "Expanding your baby's diet."* Ch. 2, p 33. Villard Books.

FDA Memorandum, "Hazards or Patulin in Apple Juice." May 5, 1994.

Fritz, W. and Engst, R. (1981) Survey of Selected Mycotoxins in Food. *J. Environ. Sci. Health B16(2)*: 193-210.

Harrison, M A (1989) Presence and stability of patulin in apple products: A review. *J Food Safety* 9: 147-153.

Hasseltine, C.W. and Graves, R.R. (1966) Microbiology of flours, *Econ. Bot.* 20: 156.

Harwig, J. et al. (1973) Occurrence of patulin and patulin-producing strains of *Penicillium expansum* in natural rot of apples in Canada. *Can. Inst. Food Technol. J.* 6: 22.

IARC (1986). Patulin, IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. 40: 8398.

Johnson, P.E. (1974) Nutrition Standards: Man, Part 1, United States: Children and Adults. Altman, P. L. & Dittmer, D.S. (ed) *Biology Data Book*, 2nd Ed. Fed Am Soc Biol. Bethesda, MD, 3: 1447.

Lehman, AJ and Fitzhugh OG (1954) Ten-fold safety factor studies. *Assoc Food Drug Officials of the US Quarterly Bulletin XVIII(1)*: 33-35.

Lovett, J., Thompson, R.G. and Boutin, B. (1975) Trimming as a means of removing patulin from Fungus-rotted apples. *J Assoc Off Anal Chem Sep*;58(5): 909-11.

Llewellyn, G.C., McCay, J.A., Brown, R.D., Musgrave, D.L., Butterworth, L.F., Munson, A.E., and white, K.L. Jr. (1998) Immunological evaluation of the mycotoxin patulin in female B6C3F₁ mice. *Food Cosmet. Tox.* 36: 1107-1115.

MAFF, Joint Food Safety and Standards Group, Food Surveillance, Number 173, April 1999.

McKinley E R, Carlton WW (1991) Patulin. In *Mycotoxins and Phytoalexins*, Ed. Sharma R P, Salunkhe D K. RC Press Atlanta.

Rubinstein, R. *Simulation and the Monte Carlo Method*. J. Wiley and Son, 1981.

Sydenham et al. (1995) Reduction of patulin in apple juice samples-influence of initial processing. *Food Control* 6: 195-200.

Ukai, T. et al. (1954) Studies on the poisonous substance from a strain of *Penicillium* (Hori-Yamamoto strain), II. Culture method of Hori-Yamamoto strain and chemical structure of its poisonous substance. *Proc. Phar. Soc. Jpn.* 74: 450.

WHO (1987) Principles for Food Safety Assessment of Food Additives and Contaminants in Food, *Environmental Health Criteria* 70.

WHO IARC (1990) Patulin. *WHO Food Additives Series*. 26: 143-165.

Hypertext updated by cjm 2000-JUN-14