establishment of a dietary concentration higher than 0.5 ppb as the threshold.

The agency does not agree that a 0.5 ppb threshold is unduly conservative, especially in light of the fact that a substance being considered for an exemption may not have been the subject of any toxicological testing. As discussed in the proposed rule, carcinogenic toxic effects in test animals typically occur at lower dietary concentrations than the levels at which noncarcinogenic toxic effects occur. Therefore, FDA's goal has been to establish a threshold that is low enough to ensure that even if an unstudied compound that is exempted from regulation is later shown to be a carcinogen, its use would not have represented any more than a negligible risk to the public health.

Although eight comments were received that expressed the opinion that the 0.5 ppb threshold is more conservative and restrictive than is necessary to adequately protect the public health, no data were provided in any of these comments to show that a threshold significantly higher than 0.5 ppb is adequate to ensure that substances present in the diet at or below the threshold would pose only negligible safety concerns. Therefore, as proposed, this final rule establishes 0.5 ppb as the threshold of regulatory concern for substances used in food-contact articles. We will reconsider this threshold if we receive new data that justify a higher level.

2. One comment objected to the agency's apparent use of a 200-fold safety factor when applying to humans the results of studies showing the noncarcinogenic toxic effects observed in animals subjected to chronic chemical exposure. The comment stated that FDA guidelines employ only a 100-fold safety factor. The comment argued that the use of the 100-fold safety factor would allow FDA to establish a threshold of regulatory concern higher than 0.5 ppb.

The agency emphasizes that it did not base its proposed threshold on noncarcinogenic toxic endpoints, and that, therefore, it did not employ the safety factor approach typically used when applying to humans the results of studies showing the noncarcinogenic toxic effects observed in animals subjected to chronic chemical exposure. Because carcinogenic effects typically occur in test animals at lower dietary concentrations than those at which noncarcinogenic toxic effects occur, as stated above, FDA's goal was to establish a threshold that is low enough to ensure that substances that are exempted from regulation under it will pose only negligible safety concerns even if they are ultimately shown to have carcinogenic effects.

Based on its analysis of the carcinogenic potencies of 477 chemicals, and using the assumptions that the distribution of carcinogenic potencies of the 477 chemicals studied are representative of all known and unknown carcinogens, and that it is very unlikely that an unstudied compound would both: (1) Be a carcinogen and (2) have an intrinsic carcinogenic potency far greater than the typical potency observed for the studied compounds, FDA has determined that, if an exempted substance present in the diet at 0.5 ppb were later found to be a carcinogen, the upper-bound lifetime risk resulting from the use of the substance is likely to be below one in a million. This level of risk is generally regarded as very low (i.e., one that poses only negligible safety concerns). Because carcinogenic effects typically occur at lower dietary concentrations than those at which noncarcinogenic toxic effects occur, an 0.5 ppb threshold would ensure that substances that pass under it pose negligible safety concerns from noncarcinogenic toxic effects as well. However, the fact that a 0.5 ppb threshold level happens to be 200, rather than a 100, times lower than the chronic exposure level at which potent pesticides induce noncarcinogenic toxic effects is merely coincidental and does not reflect the agency's reasoning.[1]

3. One comment expressed the opinion that the threshold should have been based on the mean TD_{50}[2] value of the 477 known carcinogens that were the subject of FDA analysis as opposed to the most probable TD_{50} value. This comment stated that the use of a mean TD_{50} would allow FDA to establish a threshold significantly higher than 0.5 ppb.

FDA does not agree that it is appropriate to establish a threshold level based on the mean TD_{50} value of the 477 known carcinogens that were the subject of FDA's analysis because this approach would give inappropriate weight to carcinogens with high TD_{50} values. Because the carcinogenic potency of a substance is inversely related to its TD_{50} value, this approach would give too much emphasis to carcinogens with low potencies. A more meaningful approach to estimating the likelihood that a substance will pose a potential health hazard at a given dietary concentration is to use the potency that it is most likely to have if it were later found to be a carcinogen. Because such an approach would be based on the frequency distribution of the potencies of a large number of carcinogens (i.e., a distribution showing the number of carcinogens whose potencies occur within particular dietary concentration ranges) and would not be based on the magnitude of the potencies themselves, this approach would not give undue weight to carcinogens with low potencies (i.e., high TD_{50} values).

In arriving at a threshold of regulation, FDA's analysis of the potencies of 477 animal carcinogens consisted in part of grouping them by dietary concentration ranges (Ref. 1). The agency plotted the potencies as a probability distribution on a semilogarithmic scale and found that they formed a bell-shaped distribution curve. Using this probability distribution for carcinogenic potencies, FDA determined that most known carcinogens pose less than one in a million upper-bound lifetime risk if present in the daily diet at 0.5 ppb or less.

4. One comment expressed the view that it was unlikely that a given packaging material would be present in the daily diet over the course of a lifetime. It asserted that, therefore, FDA should not have based its threshold on potential lifetime carcinogenic risks.

Because of the changing technology associated with the food-packaging industry, FDA agrees that is not always possible to predict whether a given type of packaging material is likely to be present in the daily diet over the course of a lifetime. However, because many of the substances considered for an exemption from regulation will not have been the subject of any toxicological testing, it is imperative, in establishing a threshold level, to use an approach that is not likely to underestimate the risk associated with the use of such additives. Therefore, the agency used an approach that assumed that a given packaging material would be present in the daily diet for an entire lifetime.

Lifetime upper-bound risks have traditionally been used by FDA to assess the overall safety of packaging materials containing small amounts of carcinogenic impurities, and the agency

[1] The agency typically uses a 100-fold safety factor when applying to humans the results of animal data obtained from long term exposure to a chemical (i.e., 2-year chronic feeding studies). Short term toxicological testing (i.e., 90-day subchronic feeding studies) may not always be long enough to show all of the toxic effects that may be induced by long term exposure to a chemical, and, therefore, in such cases, FDA often uses higher safety factors (1000-fold to 2000-fold).

[2] The TD_{50}, for the purposes of this regulation, is the feeding dose that causes cancer in 50 percent of the test animals when corrected for tumors found in control animals.