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ARTICLE *in* ENVIRONMENTAL SCIENCE AND TECHNOLOGY · FEBRUARY 2007

Impact Factor: 5.33 · DOI: 10.1021/es061429e · Source: PubMed

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Perchlorate in Dairy Milk. Comparison of Japan versus the United States

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Perchlorate has been considered a potential threat to human health, especially to developing infants and children due to its ability to inhibit iodide uptake by the sodium iodide symporter (NIS) of the thyroid. Although the U.S. has been the prime focus of perchlorate contamination, at least some of the similar sources of perchlorate exist across the world, and it has been detected in many types of foods and beverages worldwide. We present here perchlorate data from cow's milk samples from Japan (mean 9.4 ± 2.7 μg/L, $n = 54$), which are higher on average than those found in U.S. dairy milk samples reported by a 2004 Food and Drug Administration (FDA) study (5.9 ± 1.8 μg/L, $n = 104$).

Introduction

Perchlorate in food may lead to human exposure and possible health effects due to inhibition of iodide transport. In a recent paper, we have attempted to analyze the contributions of synthetic oxidizer-derived perchlorate, Chilean nitrate fertilizer (CNF)-derived perchlorate, and natural perchlorate deposited from atmospheric processes and other miscellaneous sources, including fireworks, to the food chain in recent decades in the U.S. (*1*). Iodine nutrition is especially important in the very young, beginning from the fetal stage (*2*, *3*). From pregnant women to young children, milk is a uniquely important food.

The first report of the presence of perchlorate in milk, in particular that all dairy milk samples bought in Lubbock, TX, contained detectable levels of perchlorate (*4*), some at levels greater than the public health goal of California in drinking water at the time, was not universally believed to be credible (*5*). Subsequently in 2004, the United States Food and Drug Administration (FDA) conducted an exploratory survey for 104 dairy milk samples from 14 states across the continental U.S., and all but three samples contained perchlorate above the limit of quantitation (LOQ, 3 μg/L), with a mean of 5.8 μg/L (*6*). Another study of dairy milk samples by us (*7*) involved 36 dairy milk samples from 18 states including Alaska and Hawaii. Although the average value of 2.0 μg/L was lower than that found in the FDA study, this study also showed the presence of detectable levels of perchlorate in 35 of 36 samples (LOQ 0.1 μg/L). Inasmuch as the FDA analyzed a substantially larger number of samples and their method used an isotopically labeled internal standard, a technique that better corrects for subquantitative recoveries in sample processing and ionization suppression in the mass spectrometer ion source, we deem the FDA values to be more reliable. We have also since adopted chromatography coupled to isotope dilution mass spectrometry after isotopically labeled perchlorate standards became available.

The presence of perchlorate in commercially grown lettuce was reported even before perchlorate was known to exist in milk (*8*); a much broader study by the FDA has confirmed the general occurrence of perchlorate in lettuce (*9*) as well as other foods, for example, cantaloupe (*10*). Others have reported the presence of perchlorate in leafy vegetables in general (*11*) and lettuce in particular (*12*), and estimated that consumption of these individual food items is unlikely to result in exposure doses in excess of the reference dose of 0.7 μg/kg-day (*11*, *12*). It has been demonstrated that a variety of forage and cereal crops will accumulate some perchlorate if the irrigation water contains it (*13*). It has been shown that citrus fruits grown with Colorado River water, contaminated with trace levels of perchlorate, also contained perchlorate (*14*). Consumption of these food items or perchlorate-contaminated water leads to human exposure to perchlorate. Indeed, human exposure to perchlorate is confirmed by the detection of perchlorate in human milk (*7*, *15*) and urine (*16*, *17*). Current analytical methods have excellent sensitivity in a variety of matrices: canned fruits and vegetables as well as beer and wine from many parts of the world have been shown to contain perchlorate (*18*, *19*). However, as compared to the detailed lettuce and milk data generated by the FDA (*6*, *9*), there are no published data in any other country on the perchlorate content of similar foods. Availability of such data will allow a better perspective of the global occurrence of perchlorate.

Why Look for Perchlorate in Japan?

The discovery of perchlorate in milk, other food products, and especially breast milk caused considerable alarm in the U.S., whether or not such concern ultimately proves to be defensible. As has been discussed elsewhere (*20*), it was not our intention to discourage anyone from breastfeeding. An understanding of any health effect of perchlorate is necessarily incomplete without consideration of iodine nutrition status. If a particular population has more than adequate iodine nutrition, intake of trace perchlorate or other iodine transport inhibitors would be relatively less important. Such information can then be discussed more rationally.

The International Council for the Control of Iodine Deficiency Disorders (ICIDD) lists only three countries with excess iodine intake based on median urinary iodine content. These are Democratic Republic of Congo, Chile, and Japan (*21*). Chile is already known to have high levels of perchlorate in the environment in parts of the country. Since the original work of Beckurts in 1886, it is known that the Chilean caliche deposits in the Atacama Desert contain significant amounts

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10.1021/es061429e CCC: $37.00
Published on Web 11/15/2006

of perchlorate. The natural presence of perchlorate prompted several toxicology studies to be conducted in Chile (*22*−*24*). Such studies have generally concluded that there are no discernible effects of perchlorate ingestion at the intake levels involved. However, the fact that the subjects may have an excess iodine intake is not accounted for: Chile is unique in that iodization of salt had to be reduced in that country (*25*).

Japan is by far the most populous of the three countries, and the status of iodine nutrition is believed to be due to the high seaweed consumption; seaweed is one of the richest sources of iodine (*26*). Whereas collecting samples from various parts in Congo would have been logistically difficult or impossible for us, we were fortunate in having friends and colleagues throughout Japan so a sampling network could be readily established and the study conducted with the limited available resources.

Japan was also attractive in that it has had only a modest space program (the first deep space probe was not successfully launched until 1998) and limited missile-related (or other major defense-related) perchlorate production since the last world war. As previously stated, three sources of perchlorate were considered in the U.S. (*1*). The first of these is synthetic oxidizer perchlorate. In recent years, a single company has essentially been the sole producer of perchlorate in Japan. In the last 5 years (2001−2005), $(6.2 \pm 0.7) \times 10^5$ kg of NH_4ClO_4 (AP, all numbers are given in terms of ClO_4^-), used mostly as propellant ingredient, and $(3.5 \pm 0.2) \times 10^5$ kg of $KClO_4$ (used for fireworks, fumigants, and explosives) were annually produced (*27*), with an additional $(5.4 \pm 1.0) \times 10^5$ kg of $KClO_4$ imported (*28*). These figures are approximately consistent with total production of 1.3×10^6 kg/y (1.6×10^6 kg/y as $NaClO_4$) in year 2000 cited by another source (*29*). Should we put this in terms of per unit land area (Japan, 3.8×10^5 km^2; U.S., 9.6×10^6 km^2 (*30*)) with a U.S. production rate of 1.1×10^7 kg/y (*1*), the potential for perchlorate dispersal is approximately 3 times greater in Japan. In addition to the perchlorate produced within the country, Japan increasingly imports fireworks from China. Even in 2003, when the imported amount was the lowest among recent years, 6.2×10^6 kg was imported (*31*). Perchlorate is a major component in many types of fireworks. However, without the exact knowledge of the types of fireworks and their rates of failure (the perchlorate contained in a device that undergoes use in the expected manner without failure is nearly completely consumed), the contribution of fireworks to perchlorate contamination cannot be quantitatively estimated. Nevertheless considering that the use of fireworks in Japan dates back centuries (*32*) and is very extensive, the contribution of fireworks to perchlorate contamination is likely non-negligible.

The dispersal of AP that occurred in the U.S. is largely armament related (*1*). A much smaller fraction of the total perchlorate used in Japan is AP, and unused armament-related dispersal should therefore be correspondingly less as compared to the U.S.

Recent data on the total import of Chilean nitrate, the second source of perchlorate, to Japan are limited. Japan was one of the first countries to be a customer of Chilean nitrate. In 1901, 2.5×10^6 kg was sold to Japan, and by 1911 this increased to 2.3×10^7 kg (*33*). However, Japan was one of the first countries to produce synthetic nitrogen fertilizers. Calcium cyanamide was commercially produced by 1909, and ammonia was produced by 1923 (and with the country's own technology by 1931) (*34*); CNF import from Chile plummeted between 1929 and 1933 (*31*). It would not appear that in recent years Chilean nitrate has made much of a contribution in Japan to perchlorate dispersal.

Atmospheric pathways for the formation of perchlorate have been shown to exist (*35*). Japan is an island nation with sea-salt aerosol in abundance and the potential to form perchlorate via either lightning or reactions with ozone. As a first approximation, we have assumed (*1*) that the natural flux is proportional to rainfall. Average rainfall over Japan during 2003 was 217 cm (*36*), ~2.6 times the average U.S. rainfall of 84 cm (*1*). The contribution from natural deposition is therefore expected to be higher in Japan.

Experimental Section

Sampling. In the U.S., the FDA sample set is comprised of 104 samples purchased in 14 states (no record was available for specific locations within the states (*37*)), and except for some raw milk (*3*), skim milk (*2*), 1% fat (*7*), and 2% fat (*1*) samples, all others were whole milk samples. There was no discernible relationship between the fat content and the perchlorate content; we did not therefore attempt to obtain a fat-content matched sample set in Japan.

Japan is divided into 47 local jurisdictions often referred to as the Tōdōfuken system (*38*): Tokyo (Tō) and Kanagawa, Saitama, and Chiba prefectures, one circuit (dō), Hokkaido, urban areas, Osaka and Kyoto (fu)s and Hyogo prefecture, and other urban/rural prefectures (ken). Our volunteer collaborators randomly bought 54 samples in August−September of 2005 from 48 different locations that included Tokyo, Hokkaido, Osaka, Kyoto, and 20 rural prefectures. Much as in the U.S., milk is generally not transported over long distances in Japan. Milk sold in stores is typically of regional origin. Aside from some samples containing ≤1% fat (*12*), some with 1−2% fat (*5*), and one sample where fat content was not specified, all others had ≥3% fat. The samples were shipped by "cold-pak" courier mail to the author's laboratory at Kinki University where it was stored at −30 °C until processed (generally in ≤3, always <4 weeks).

Milk Processing Method. The milk processing method is a streamlined procedure that has been described in detail elsewhere (*39*). However, available equipment dictated some changes, notably in centrifugation condition and duration. Briefly, 20 mL of the milk sample was put in a 50-mL capacity centrifuge tube and spiked with 100 μL of $NaCl^{18}O_4$ (Icon Isotopes Inc.) containing 1 mg/L $Cl^{18}O_4^-$ to function as a 5 μg/L internal standard. The samples were centrifuged in sets of 8 at 16 000 rpm at 15 °C for 25 min (KR-20000T, Kubota Corp.) to remove the fats and cream from the milk. The latter floats up to the top to a solid mass, and the liquid below is decanted to the top part of a prewashed PL-10 Centricon Plus-20 centrifugal filter device (Millipore Corp., P/N UFC2 LGC 24). The Centricon devices were twice centrifuged at 3000 rpm at 15 °C for 90 min (Himac CF7D2, Hitachi Corp.). About 9−14 mL of the liquid dialyzes through the filter, the amount generally decreasing with increasing fat content of the milk. A 0.5 g aliquot of prewashed Amberlyst 15 macroreticular cation-exchange resin (Aldrich P/N 06423) was added to the dialyzate; the sample was vortexed for 5 min and allowed to stand for 10 min. The sample was then taken into a prewashed 10-mL disposable syringe and passed through a prewashed 25 mm, 0.45 μm pore size nylon membrane syringe filter and the filtrate divided approximately equally into two prewashed prelabeled autosampler vials (Dionex P/N 038141) and stored at −30 °C until shipment. In independent experiments in the U.S., it was verified that there is no discernible degradation of perchlorate in such processed samples over 1 week at room temperature, whether in the dark or exposed to sunlight. The processed samples were air-shipped to the author's laboratories at TTU.

Analysis. All chromatography was performed on a DX-600 ion chromatograph (GS50 gradient pump, ASRS-Ultra 4-mm suppressor, CD25 conductivity detector, PeakNet 6.2 chromatography software, peak area-based analyte quantitation). The preconcentration-preelution method developed by Tian et al. (*40*, *41*) was used with minor modifications. Separation was performed on a Dionex IonPac AG-16 (4 ×

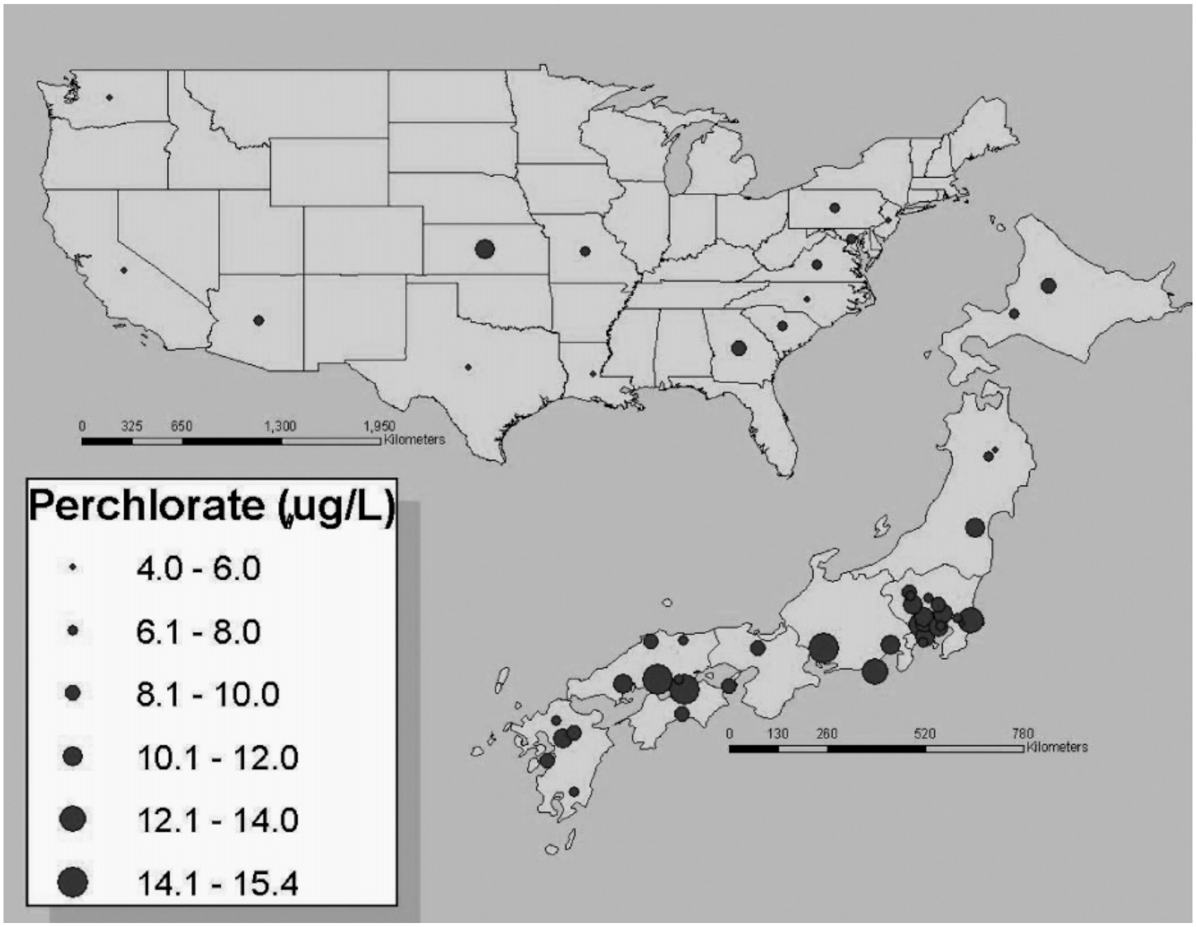

FIGURE 1. Distribution of perchlorate in dairy milk, U.S. versus Japan. U.S. data from ref *6*. See detailed data from Japan in Supporting Information Table S1.

50 mm) guard column and IonPac AS-16 (4 × 250 mm) anion separation column. A TAC-LP1 (4 × 35 mm) anion concentrator was used as a preconcentration column (PCC). The injection loop volume was 1 mL. As the pre-eluent (wash solution), 5 mM NaOH was used at a flow rate of 0.85 mL/min for 2.5 min prior to injector switching, and the main eluent (100 mM NaOH at 1 mL/min) then eluted the analyte anions of interest to the separation column.

A Thermoquest-Finnigan AQA mass spectrometer (MS) was used in the electrospray ionization mode. The MS data were acquired using the Xcalibur version 1.1 software package. The mass spectrometric detection of perchlorate was aided by ion pairing the perchlorate ion postcolumn with D^{2+} derived from 1,12-bis(trimethylammonium) dodecane difluoride DF_2 (*42*). The effluent from the column was split to allow 60% of the flow to the MS and 40% to waste. A syringe pump (V6, Kloehn Co., Las Vegas, NV) introduced 100 μM DF_2 at 60 μL/min to mix with the effluent before entering the MS. The ESI-MS probe temperature was set at 350 °C and the ionization potential at 3 kV. The MS operated in the selective ion monitoring mode (SIM). The monitored ions had m/z ratios of: 384.8 ($D^{35}Cl^{16}O_4^+$), 386.8 ($D^{37}Cl^{16}O_4^+$), 393.0 ($D^{35}Cl^{18}O_4^+$), 395.0 ($D^{37}Cl^{18}O_4^+$). Perchlorate was quantified using the area ratio of the m/z 384.8 peak to the internal isotopic standard peak at m/z 393.0. We also monitored m/z 344.0 ($D^{32}SCN^+$) and m/z 413.0 (DI^+). Concentrations of iodide are obviously important when considering iodine nutrition or the effects of iodide transport inhibitors thereupon. Thiocyanate was measured because, after perchlorate, it is the next most potent iodide transport inhibitor. These results are given in the detailed results data table (Table S1; S1, S2, etc. represent documents in the Supporting Information); however, these data are not further discussed.

Results and Discussion

Perchlorate Concentrations in U.S. and Japanese Dairy Milk. All Japanese samples (n = 54) were above the LOQ, had a range of 5.47−16.40 μg/L, a mean (± standard deviation) of 9.39 ± 2.71 μg/L, and a median value of 9.34 μg/L. In comparison, of 104 U.S. samples in the FDA data set, three had detectable levels of perchlorate that were below the LOQ (3 μg/L), and one-half that value was taken by the authors to be the concentration for these samples for statistical purposes. This resulted in a range of 1.5−11.3 μg/L, a mean (± sd) of 5.74 ± 1.98 μg/L, and a median value of 5.56 μg/L. The comparability of the mean and median values indicates that in both data sets the results are reasonably symmetrically distributed. The values in Japan appear to be higher than the U.S. values (ratio of averages 1.64) to a very high degree of confidence ($p \leq 0.00001$). Table S1 in the Supporting Information provides the full results for the Japanese samples. Figure 1 shows the comparative results in a graphic form. For the highest measured perchlorate concentration of 15.3 μg/L, consumption of 1 L of this milk a day by a 70 kg adult will represent ~31% of the reference dose of 0.7 μg/kg-day. For an infant that consumes 100 mL milk/kg-day (*43*), the reference dose would be exceeded at the average measured concentration of 9.4 μg/L. However, the reference dose does not take any account of the excellent iodine nutrition in Japan. Although many more sample data were available for the U.S., without any information on the specific intrastate origin of the different samples, we could only plot the average for each state sampled. The detailed data are readily accessible through the web (*6*).

Dispersal of Perchlorate. Perchlorate in Milk. Perchlorate in dairy milk should be a function of perchlorate intake by the dairy cattle from water and feed. Note that, as compared to a lactating human mother, a dairy cow produces 5−7 times more milk per unit food input and also consumes proportionately more water (*7*). This suggests that perchlorate intake from feedwater is relatively more important for dairy cattle than for humans. Drinking water for cattle is always of local origin, and about one-half of the feed tends also to be of local or at least regional origin (vide infra). This means that the perchlorate content of milk should be closely related with perchlorate dispersed in the local environment. There are no data in Japan specifically on the regional dispersal of perchlorate. In the U.S., the EPA has compiled data of known releases, and a table of highest concentrations of perchlorate measured in drinking water, groundwater, surface water, and soil is available (*44*). Naturally, even in the best cases the data density is poor. For the 10 states (AZ, CA, KS, MD, MO, NJ, SC, TX, VA, WA) in this listing for which milk data are also available from the FDA (with the same problem of insufficient coverage, sometimes only 1−2 samples for the whole state), we have compiled the available data in a Supporting Information table (Table S2). While there is good correlation between perchlorate concentrations in milk and in surface water, this is largely meaningless as there are only three data points. There are five or more points for testing correlation with milk perchlorate only for groundwater and soil. Also, as can be observed in Table S2, there is no meaningful correlation between the highest dispersed perchlorate concentration (either for groundwater or for soil) with either the average, or the highest perchlorate concentration of milk in that state. This is not surprising as most of the contamination data come from relatively highly contaminated sites owned and operated by the Department of Defense and one would not generally expect dairy cattle to graze there. The limited amount of dispersal data that exists in the U.S. is therefore too scant to be meaningful.

Can perchlorate intake be linked to the dietary intake of the cows? In Japan, lactating dairy cows are fed rations at 15−25 kg dry matter per day, according to the recommendations of Japanese feeding standards (*45*). The rations for dairy cows are usually composed of 40−60% of concentrates, the remainder being forage to satisfy both their nutrient requirements and recommended fiber content (*45*). The main ingredients in the concentrates (formula feeds) for dairy cows are corn (40%), soybean meal (12.3%), byproduct feeds (11.8%), barley (1.9%), and grain sorghum (1.7%) (*46*). Interestingly, these feeds are mostly imported from the U.S. Japan annually imports approximately 1.5×10^{10} kg of grain as feed (*46*). U.S. products contribute 96%, 70%, 27%, and 21% of imported corn, grain sorghum, barley, and soybean meal, respectively (*47*). Japan self-supplies approximately 75% of total forage consumed, the remainder being mainly supplied by the U.S. According to public statistical data, U.S. products account for 82% of the imported alfalfa (total import 4.3×10^8 kg) and 73% of the hay (total import 2.0×10^9 kg) (*43*). Iodine intake is also recommended in the feeding standards (0.60 ppm in diet) (*43*). According to these statistical data, it is estimated that 30−50% of the feed given to Japanese lactating cows originates in the U.S. The part of the food imported from the U.S. cannot obviously account for perchlorate concentrations higher than those of U.S. milk and suggests that the perchlorate concentration in the Japanese feed or the water given to the cows is higher in Japan than the corresponding values in the U.S.

We believe that these results show that the presence of perchlorate in milk (and possibly other foods) is hardly unique to the U.S., consistent with other recent reports (*18*). Perchlorate concentrations in milk in Japan are higher than (or at least comparable to) those in the U.S. This may be accounted for by higher production rate per unit area (with a proportionately higher dispersal), higher natural deposition through greater rainfall, and possibly greater use of fireworks. Japan is fortunate to have excellent iodine nutrition (*48*−*50*); the same cannot be said for many other countries (*21*).

Acknowledgments

P.K.D. thanks many friends in Japan without whose help it would have been impossible to carry out this work. We thank Icon Isotopes Inc. for the grant-in-aid of the isotopically labeled perchlorate standard. Dr. Alex Krynitsky of the USFDA and Kevin Mayer of the USEPA and Balaji Rao of Texas Tech University Department of Environmental Engineering are thanked for their help. We acknowledge the support of Dionex Corp., both directly and in the form of analytical consumables. This work was supported from the Paul W. Horn Professorship funds to P.K.D. at TTU. We acknowledge all of the following people who procured and took the trouble to package and ship the samples and paid such shipping costs; without their generous help this study would not have been possible: Drs. Shin-Ichi Wakida and Sahori Takeda, AIST, Osaka; Dr. Takashi Hayashita, Sophia University, Tokyo; Akira Tanaka and Drs. Kei Toda and Shin-Ichi Ohira, Kumamoto University, Kumamoto; Drs. Hideharu Shintani and Mitsunori Murayama, National Institute of Hygienic Sciences, Tokyo; Dr. Hideji Tanaka, Tokushima University, Tokushima; Mutsumi Usui, Arc Science, Tokyo; Dr. Testsuo Okada, Tokyo Institute of Technology, Tokyo; Dr. Osamu Nara, Tohoku Pharmaceutical University, Sendai; Drs. Tadao Sakai and Norio Teshima, Aichi Institute of Technology, Nagoya; Drs. Shoji Motomizu and Toshio Takayanagi, Okayama University, Okayama; Dr. Kiyoko Takamura, Tokyo University of Pharmacy and Life Sciences, Tokyo; Dr. Kin-ichi Tsunoda, Gunma University, Kiryu; Dr. Manabu Igawa, Kanagawa University, Yokohama; Dr. Keiko Kurita, Tokyo Metropolitan Industrial Technology Research Institute, Tokyo; Yuki Ito, Hiroshima; and Kazuko Hisamatsu, Tokyo.

Supporting Information Available

Additional information as noted in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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Received for review June 15, 2006. Revised manuscript received September 14, 2006. Accepted October 9, 2006.

ES061429E