AUTHOR'S REPLY,—Samy Suissa and colleagues raise three issues. Firstly, they suggest that the relative risk of 2·0 for fenoterol explains only a small proportion of the epidemic. Our study was based on prescribed drug treatment rather than that actually taken[1]; this non-differential information bias would tend to decrease the observed odds ratios towards 1·0.[2]

Secondly, they suggest that the epidemic could have been due to overuse of all inhaled ß agonists. A similar error was recently made by Staudinger and Haas.[3] In fact, sales of all ß agonists in New Zealand increased considerably only after 1979, three years after the onset of the epidemic,[4] in response to suggestions that ß agonists should be used regularly rather than on demand. The large relative risks for all ß agonists in the Saskatchewan study emerged only in the questionable multivariate analysis,[5] and probably tell us more about overuse of multivariate analysis than overuse of ß agonists.

Thirdly, they argue that mortality was declining anyway and the dramatic fall in mid-1989 is not significant, a point echoed by Jeff Garrett. Mortality declined during 1979-83 (after the epidemic was publicised) but remained relatively constant during 1983-8. Mortality remained high during the first half of 1989, whereas in the second half (after warnings about the use of fenoterol) it fell significantly (p=0·04) to one half of the level of the preceding six years. The analysis by Garrett seems to be based on a regression of the plotted points which does not take into account statistically the number of deaths on which each point is based. This methodological error produces absurdly wide confidence intervals that encompass the whole epidemic, and the elimination of all deaths from asthma would not be significant. Suissa and colleagues' analysis is also in error in examining yearly fluctuations which exhibit extra-Poisson variation due to non-random influences such as warning and publicity about the epidemic.

Thus the time trend data are consistent with the fenoterol hypothesis (supported by four case-control studies[1 6 7] and experimental evidence[8 9]) but are inconsistent with the hypothesis that the epidemic was due to a class effect of all ß agonists.

Finally, we take exception to Garrett's claim that we have misrepresented recent mortality trends. We have presented the data in exactly the same format as used previously,[1] but added recent data to assess the effect of the "natural experiment" of warnings and restrictions on fenoterol.

The other issues that Garrett raises have already been addressed in our reply[10] to a similar letter[11] in the *New Zealand Medical Journal*. We have repeatedly found that fenoterol was not selectively prescribed to patients with more severe asthma in the population of patients with asthma recently admitted to hospital whom we studied (the situation may be different in countries like the Netherlands, where fenoterol's market share was only 2-3%[12]). Garrett has responded to this extensive evidence by simply repeating his original claims.

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Vitamin K and childhood cancer

EDITOR,—David Hull suggests that doctors should be confident that oral administration of vitamin K is as effective as the intramuscular injection in preventing haemorrhagic disease of the newborn before changing their practice to avoid the risk of causing later childhood cancers.[1] We agree that the increased risk of haemorrhagic disease of the newborn if vitamin K is not given is nearly certain whereas the association with childhood cancer is not, but this does not mean that doctors should wait until they are equally certain about possible harmful effects of the intramuscular route before changing to oral administration. The decision should depend on the severity of the bad outcomes, the absolute size of the putative risks, and the degree of certainty that these risks are true.

Childhood cancer is at least as bad an outcome as late haemorrhagic disease of the newborn, and many would rate it as worse. The sizes of the risks, however, are very different. The table summarises the estimates given by Jean Golding and colleagues[2]: if they are true a massive increase in cancer is traded off against a small decrease in haemorrhage, according to the route of administration of vitamin K. How certain are we that the intramuscular route causes cancer? The data from the original study that generated the hypothesis have been confirmed by a large prospective study, albeit by the same authors. Childhood leukaemia did increase in the 1960s, around the time that intramuscular vitamin K was introduced. On the other hand, case-control studies are notoriously susceptible to subtle bias.

It is unlikely that we will ever disprove the suggested association between intramuscular vitamin K and cancer by means of a prospective trial. We have to act on other information and hence a lower probability that any observed effect is real. It is important that we do not wait until we are absolutely certain about the big absolute increase in risk of cancer before forgoing a smaller, albeit certain, protection against haemorrhagic disease of the newborn. An observer might be 20% certain (p in the table) that the association is at least as big as measured (a relative risk of 2). Such an observer should withhold intramuscular treatment, not wishing to trade a 20% belief that it causes 980 cancers against 100% belief that it prevents nine cases of late haemorrhagic disease of the newborn. Such an observer's degree of belief (p) would vary as new data became available, perhaps using the technique of bayesian inference.[3]

If a group of babies such as those born prematurely had a particularly high risk of haemorrhagic disease of the newborn then the balance of risks for that group may be different and perhaps the intramuscular route should be retained for them. Conversely, for term babies the risk of haemorrhagic disease of the newborn from oral administration may be lower than the risks given in the table and the balance of risks more strongly weighted against the intramuscular route.

Public health decisions, like clinical ones, are right or wrong in prospect, not retrospect. Empiricists should be no more reluctant to abandon a treatment than to forgo its introduction at a given state of knowledge. Would we switch from oral to intramuscular vitamin K given the current evidence?

Effect of oral versus intramuscular vitamin K on late haemorrhagic disease of newborn and cancer in childhood (No of cases) in 700 000 babies

	Oral	Intramuscular	Certainty factor (%)†
Late haemorrhagic disease of newborn	10	1	100
Childhood cancer	980	1960*	p

*95% Confidence interval 1274 to 2940.
†Our subjective probabilities that the effects are as great as or greater than those observed (that is, that the relative risk is 10 for haemorrhage with oral vitamin K and 2 for cancer with the intramuscular route).

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Coloured inhalers

EDITOR,—Minerva mentions again the problems of asthma inhalers being provided in several different colours.[1] The traditional concept of blue being for relievers and brown or red for preventive medicines is now totally confused by, for example, the arrival of a generic salbutamol in a brown inhaler. This makes patient education difficult and also causes problems when giving advice to others, such as schoolteachers, who care for those with asthma.

I have a file on this subject going back to 1984. We have discussed the problem with the Department of Health and written on numerous occasions to both the Association of the British Pharmaceutical Industry and to the Medicines Control Agency. We have extolled to them either the virtues of a rough standardisation of colours, or the application of a mark such as a circle for relievers and a cross for preventers. Despite these numerous dignified and justifiable representations, we repeatedly receive replies to the effect of "there can be no substitute for carefully reading the label before any medicine is taken." Such a reply can only have been written by someone with no experience of the difficulties involved in patient education in this common condition.

There is essentially only one purchaser of drugs in this country and it seems incredible to us that the current dangerous confusion is allowed to continue. If your readers agree with us, perhaps they could also write to the Association of the British Pharmaceutical Industry (12 Whitehall, London SW1A 2DY) and Medicines Control Agency (1 Nine Elms Lane, London SW8 5NQ), and if they send a copy of their letter to me, I will ensure that the Department of Health is kept informed of the strength of this opinion.

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