21 September, 2004.

The General Manager
Pfizer Consumer Health Care
P.O. Box 3998
Auckland

Attention: Mr Peter Baltus

Dear Mr Baltus

Thank you for your letter dated 15th September, 2004.

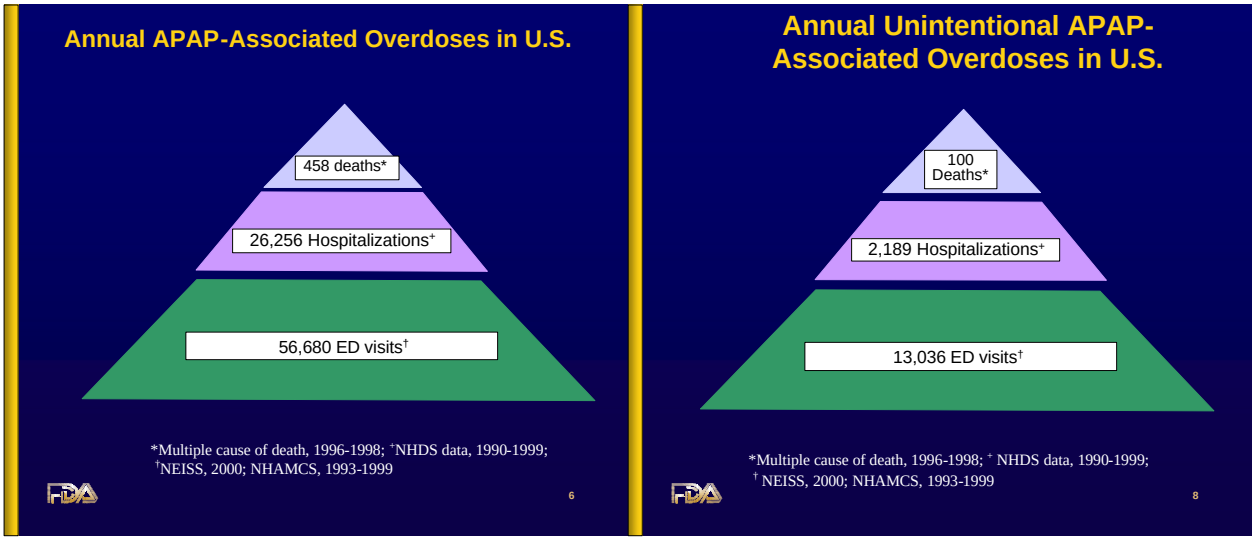
While the Immunisation Awareness Society (IAS) acceded to Pfizer's reasonable request for us to retract statements that we made, and to in future not to name a proprietary product registered to that company, by the name of Pamol®, we question what might be perceived as harassment of the society. IAS believes that Pfizer's further requests call into question key issues.

First is the issue of why Pfizer is now demanding that IAS in no shape or form mention the generic term paracetamol (*N*-acetyl-*para*-aminophenol).

Secondly is the issue of the science behind Pfizer's claims.

According to the FDA,[1] paracetamol isn't safe for some people (refer to graphs on this and the following page). As the accompanying *British Medical Journal* report infers (see page 4), pharmaceutical companies apply pressure in order that they are not "offended". As the *British Medical Journal* text shows, there is considerable concern about the safety and formulation of paracetamol.

And as IAS knows, Pfizer wants us to drop our comments, because it finds them offensive.



[1] FDA. http://www.fda.gov/ohrms/dockets/ac/02/slides/3882S1_05_Nourjah-Ahmad-Karwoski.ppt

Summary of Calls

- APAP-related calls represents 10% of all 1999 calls to PCCs
- Calls slightly decreased from 111,175 in 1995 to 108,102 in 1999
- In 1999
  - about 50,000 (46%) calls were treated in health care facilities
  - 1,768 (2%) of the calls had major effect*
  - >50% calls in children (≤ 19 years)

*Signs or Symptoms occurring as a result of the exposure were life threatening or resulted in significant residual disability

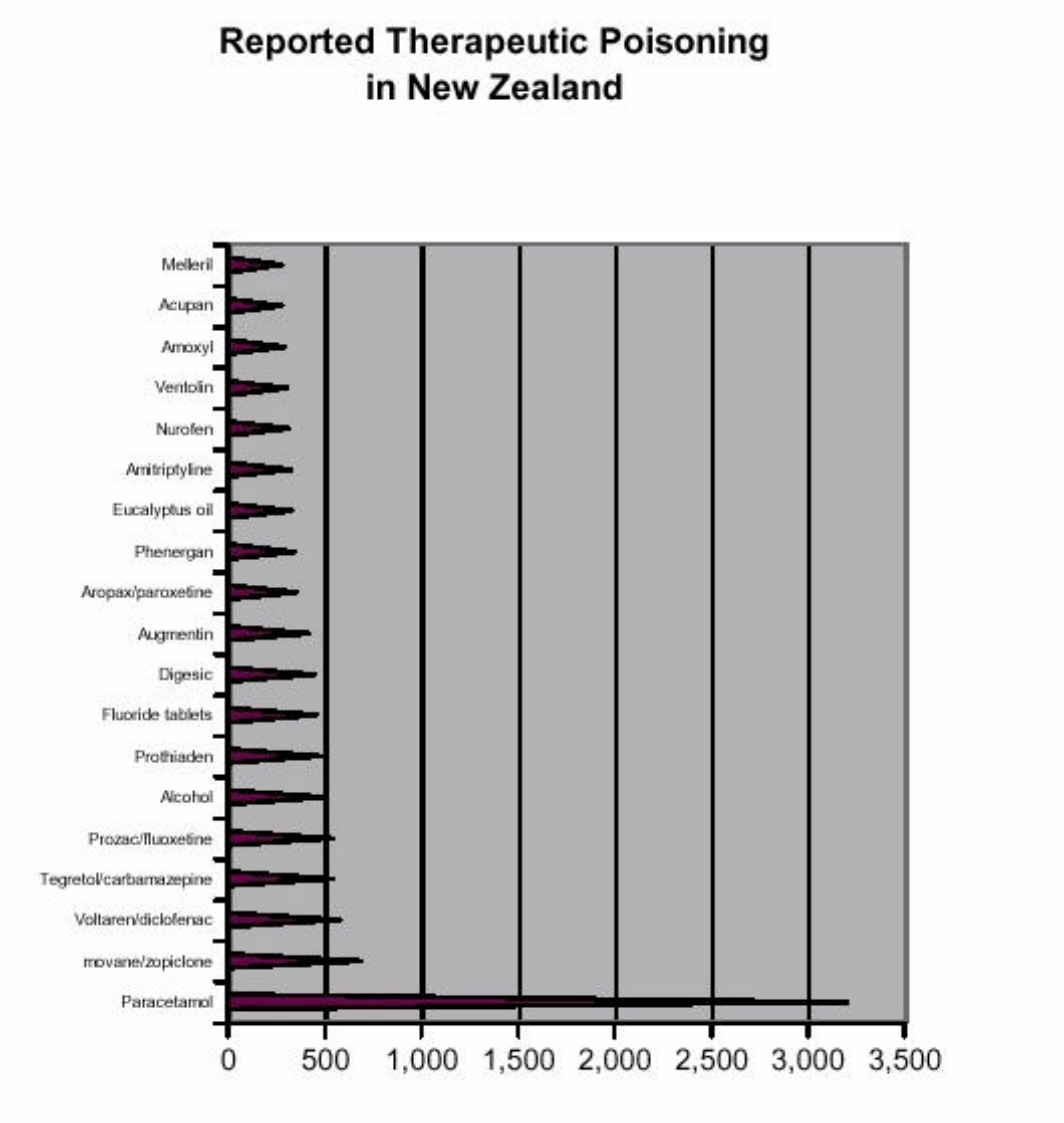
22

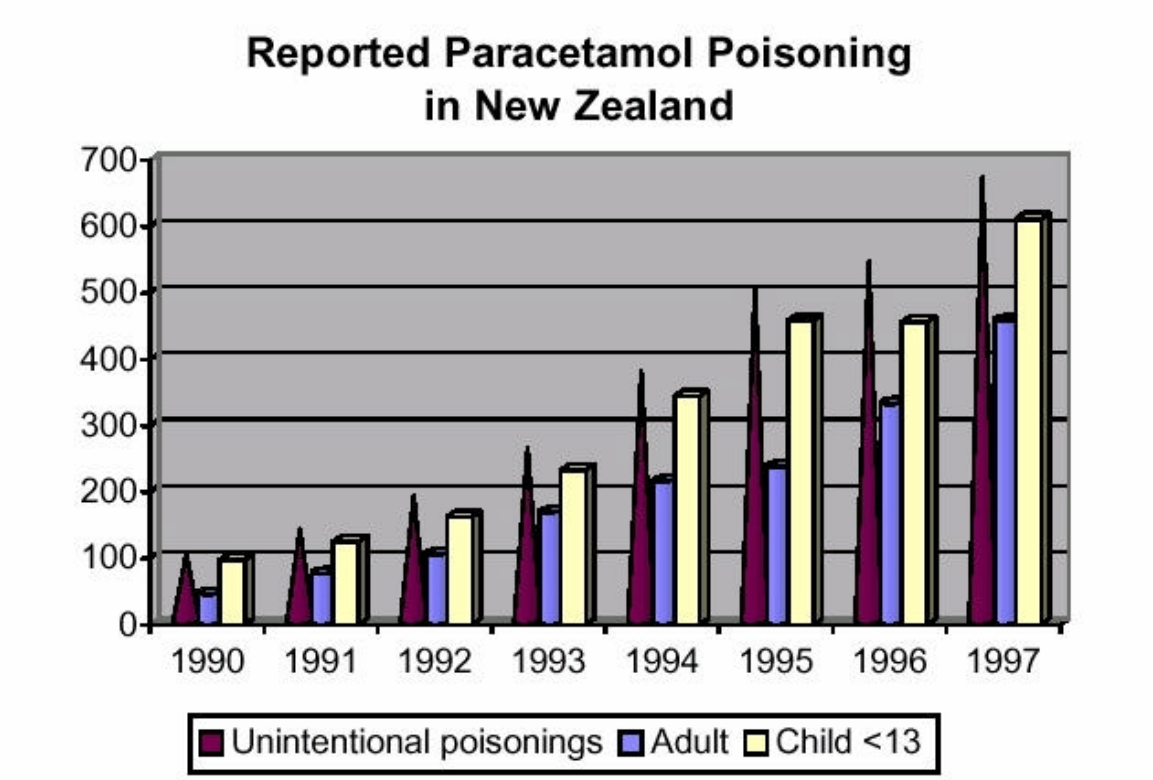
Root Cause Among Children, 1999

- Of all APAP related calls in children under 6 years (N=40,105)
  - 8,634 (22%) involved children under 6 years of age who ingested adult formulations

23

IAS acknowledges that these are USA data, so we have sourced information from the New Zealand National Poisons Centre as follows:





FDA fails to reduce accessibility of paracetamol despite 450 deaths a year[2]

"Confidential documents from the US Food and Drug Administration suggest that the agency has avoided a debate on tough new measures to reduce overdoses from painkillers **to avoid offending the pharmaceutical industry**. Ray Moynihan reports from Washington, DC.

"A confidential draft document reveals that the Office of Drug Safety also wanted the advisory panel to discuss whether the "maximum tablet strength should be decreased," whether "**combination products be reformulated without acetaminophen**," and whether there was "**a need to standardize the various paediatric formulations**.

The advisers never saw that draft, however, and none of these key options ended up being clearly presented to the committee by the FDA in the final list of questions they were to consider.

Acknowledging an unusual level of confusion throughout the hearings, the advisory committee's chairman, Dr Lou Cantilena, said in an interview afterwards that the questions supplied by the FDA were too vague. "The committee would have preferred more focused questions," he said.

According to one FDA insider, **the draft questions were dropped because senior FDA managers saw them as too offensive to Johnson & Johnson**. Asked about this alleged corporate influence within the FDA, Dr Cantilena smiled and said he did not want to speculate."

The FDA refers to acetaminophen (paracetamol) as a drug with limitations…[3]

"Due to potential liver problems, these are some drugs that have significant limitations on their use (warnings, dose restrictions, monitoring):
Niaspan Extended Release Tablets (niacin)
Dantrium (dantrolene)
Tylenol (acetaminophen)
Normodyne (labetalol)
Cylert (pemoline)

[2] *BMJ* 2002;325:678 (28 September) http://bmj.bmjjournals.com/cgi/content/full/325/7366/678,
[3] http://www.fda.gov/fdac/features/2001/301_liver.html

Felbatol (felbamate)
Zyflo (zileuton)
Tasmar (tolcapone)
Trovan (trovafloxacin, alatrofloxacin)"

There is sufficient concern regarding the hazards of paracetamol use in children that questions are being asked in New Zealand research regarding the use of paracetamol.[4]

We also note that Pamol® products carry a caution: ***Do not give to children under 2 years of age except on medical advice. Prolonged use can be harmful. Do not use for more than 48 hours with out seeking medical advice.***[5]

Therefore, there are significant safety issues associated with the use of paracetamol.

USE OF LEADING BRAND NAMES IS COMMON

IAS got caught up in a common practice of using leading brand names in lieu of generic drug names[6,7] (for example, Sandra Patterson in the *New Zealand Herald*, 8 August 2004).[8] For using a brand name in lieu of the generic drug name IAS has already unreservedly apologised.

THE RIGHT OF IAS TO USE THE WORD "PARACETAMOL".

IAS questions Pfizer's primary motivation for its current letter. Or the previous letter, for that matter, but our current concerns primarily arise from Pfizer's latest demands that IAS not mention in any way, the generic NON-PROPRIETARY compound PARACETAMOL, if it would imply that it is associated with the increased risk of developing any disease, or is detrimental, or otherwise harmful.

IAS actioned the requests made in Pfizer's first letter in good faith and we believed that those requests were acceptable, in that we acknowledged that we should not have specifically named Pfizer's registered, proprietary brand name, specifically PAMOL®, marketed by Pfizer.

However, our current advice is that Pfizer have no legal or patent standing which would entitle it to prohibit the use of the generic term "paracetamol". This position is acknowledged in the medical literature.

BMJ should use "paracetamol" instead of "acetaminophen" in its index[9]

"Acetaminophen is the United States adopted name,[4] and in the United States the substance is always and only called acetaminophen. **Paracetamol is the recommended international non-proprietary name**,[4] the British approved name,[4] and the name used for the substance throughout the world outside the United States."

We put to Pfizer a series of questions, to which we request that we receive fully referenced, comprehensive answers by 5.00 p.m., Wednesday, 29th September, 2004. Given that Pfizer consider

[4] http://isaac.auckland.ac.nz/Phasethr/EnvrQuest/Instr6_7.html
[5] http://www.onlinepharmacy.co.nz/index.cfm/layout/Brand/BrandID/300/CatID/14
[6] http://www.polyhigh.org.nz/index_files/efa.pdf
[7] http://www.fda.gov/fdac/features/2001/301_liver.html
[8] Sandra Paterson, Vaccination: tell me more, *New Zealand Herald*, 8 August, 2004, http://www.nzherald.co.nz/storydisplay.cfm?storyID=3582728&thesection=news&thesubsection=dialogue
[9] *BMJ* 1996;313:689 (14 September) http://bmj.bmjjournals.com/cgi/content/full/313/7058/689

three working days sufficient time for IAS to respond to your letter, with the ample staff available to Pfizer, IAS is sure you will find such a dead-line acceptable.

1) QUESTION: Please provide for us, the legal standing upon which you can require IAS to never use the term PARACETAMOL at any time in the future, in anything we say, or publish?

Pfizer's 15 September, 2004, letter imposes further demands on IAS. The legitimacy of these demands are highly questionable. These issues are:

TREATMENT OF CHILDREN.

In your letter, page one, first paragraph Pfizer states:

"Pfizer ***demands*** that IAS undertakes not to provide any information in the course of interviews, public statement, or publication (including information available from the IAS website) **which would tend to suggest or imply:**

…

b) that the use of Pamol or paracetamol in the treatment of children is detrimental."

Please consider the following information carefully before you fully, and comprehensively answer all of the following questions:

The Neurologic basis of fever[10]

Page 1880:

"The ***elevation of body temperature by a few degrees may improve the efficiency of macrophages*** in killing invading bacteria, whereas ***it (fever) impairs the replication of many microorganisms, giving the immune system an adaptive advantage***.

There is a simultaneous switch from the burning of glucose, an excellent substrate for bacterial growth, to metabolism based on proteolysis and lipolysis. The host organism also becomes anorexic, which minimizes the availability of glucose, and somnolent, which reduces the demand by muscles for energy substrate. ***During the febrile response, the liver produces proteins known as acute-phase reactants. Some of these proteins bind divalent cations, which are necessary for the proliferation of many microorganisms.***

The net effect of the metabolic responses activated during fever is to give the host organism an adaptive advantage over the invader."

Page 1883:

"IMPLICATIONS FOR MEDICAL PRACTICE

Should fever be treated? There is a strong tendency for physicians to treat fever as an abnormal pathologic condition that should be corrected as quickly as possible. In fact, consideration of the mechanisms of fever indicates that in the absence of brain injury, it is a normal and adaptive physiologic response. Although very high body temperature (above 40°C) can clearly injure both the central nervous system and other body systems, an argument can be made that low grade fevers

[10] Saper, Clifford B., *The New England Journal of Medicine*, vol. 330, No. 26. June 30, 1994,

(below 39°C) probably should not be treated unless they make the patient so uncomfortable ***that it appears wise to sacrifice the adaptive advantage of the febrile state***."

2) QUESTION: If the febrile state has biological and immunological ***advantages*** to anyone with a fever, why would anyone wish to ***sacrifice the adaptive advantage*** of them by the administration of any antipyretic? Is this not potentially "detrimental" to the patient?

Antipyresis and Fever[11]

Page 1589:
"Antipyretic drugs are effective in diminishing fever**, but they have significant side effects and may suppress signs of ongoing infection**."

"**Antipyretic therapy should not be instituted routinely** for every febrile episode but should be based on evaluation of relative risks in the individual case and reassessed if anticipated benefits are not achieved."

3) QUESTION: If antipyretic drugs "have significant side effects and may suppress signs of ongoing infection" why does Pfizer consider that the routine use of such products is **not** detrimental to children?

"Antipyresis is one of the oldest, most common, and **most *automatic* therapeutic interventions** undertaken. The objective of this review is to provide an informed basis for decisions on whether and when fever should be treated"

"It is commonly acknowledged that physicians often treat fever to alleviate anxiety in patients, their families, or medical personnel, and that **such treatment often lacks a compelling medical rationale**."

4) QUESTION. If the AUTOMATIC use of antipyretics **often lacks a compelling medical rationale**, and is often used to relieve the anxiety of parents or doctors, why does Pfizer consider such a reason for a prescription "clinically appropriate"?

Pg 1594:
"The decision to administer antipyretics is frequently made ***without a documented rationale***. Current understanding of the mechanisms and pathogenesis of fever suggests that the febrile process has a role in host defense and that **routine antipyretic therapy for fever is generally unnecessary and conceivably harmful.** "

5) QUESTION. If this highly respected medical journal can state that **routine antipyretic therapy for fever is generally unnecessary and conceivably harmful**, on what legal grounds does Pfizer now demand that IAS never quote, state, or imply what is clearly set out in the medical literature? (That is, that the use of antipyretics often lacks compelling medical rationale, is prescribed for non-medical reasons, and has potential dangers to the person taking it.)

"Decisions to attempt suppression of fever should be based in infrequent indications arising in an individual case **and should take into account the potential risks of antipyresis as well as its often questionable benefits**."

Pg 1594:
"In the vast majority of febrile illnesses**, there is no evidence that fever is detrimental or that antipyretic therapy offers any significant benefit**. Indeed, the limited information available on *in*

[11] Barbara Styrt, MD, Barrett Sugarman MD. *Arch Intern Med* – Vol 150, August 1990,
(Archives of Internal Medicine is a peer reviewed paper)

vitro immune functions and *in vivo* outcomes would suggest that fever usually does more good than harm."

6) QUESTION: If this highly respected doctor states that there are risks, and that there is **no evidence that antipyretic therapy offers any significant benefit** (and also implies that to allow the fever does more good than harm), on what basis does Pfizer imply, or wish IAS to imply, that the routine use of anti-pyretic treatment of children is useful or beneficial?

"In treating fever "symptomatically" one should not lose sight of the fact that elevated temperatures, whatever their physiologic function, do serve as a signal both to the patient and to the caregiver. **Nonspecific suppression of fever may deprive one of clues to a need for further diagnostic investigation, or for changes in therapy**. Although these clues will often occur in the context of antipyretic use, one study has indicated that **patients with a variety of bacterial infections receiving antipyretics experience a significant delay in institution of needed antibiotic changes**."

Severity of disease correlated with fever reduction in febrile infants.[12]

"A prospective study of the effects of fever reduction on the clinical appearance of infants at risk for **occult bacteremia** was undertaken to study the hypothesis that infants with bacteremic illness fail to improve clinically following defervescence compared with infants with benign viral illness. A total of 154 children were enrolled in the study, including 19 with bacteremia: 13 with occult Streptococcus pneumoniae bacteremia, two with occult *Haemophilus influenzae*, type b bacteremia, and four with Haemophilus meningitis and bacteremia. ***There were no differences in degree of temperature reduction with acetaminophen between the bacteremic and nonbacteremic groups of infants***. Among infants with bacteremia but without meningitis, ***differences from nonbacteremic children were detected in clinical appearance prior to fever reduction but not following defervescence***. All patients with meningitis appeared seriously ill before and after defervescence. It was concluded that clinical improvement with defervescence is not a reliable indicator of the presence of occult bacteremia. Lack of clinical improvement with defervescence may be a reliable indicator for the presence of meningitis. **Because there were differences in clinical appearance prior to fever reduction, routine administration of acetaminophen may interfere with the clinical evaluation by the physician.**

7) QUESTION: If doctors can state that **patients with bacterial infections treated with antipyretics can experience significant delays in institution of needed antibiotic changes**, and may interfere with clinical evaluation by a physician, could not the use of paracetamol, be considered a "harm" to the child?

New concepts on the pathogenesis of fever[13]

"***Elevated body temperature enhances the inflammatory response and function of the immune system*** at the same time that it reduces the replication of microbes and tumor cells."

Impact of Temperature Elevation on Immunologic Defenses[14]

Page 469:
"Overall, it appears that ***temperature elevation within the physiologic range most effectively enhances the processes involved in initial antigen recognition and support for immunologically specific response to challenge***."

[12] *Pediatrics.* 1989 Jun;83(6):1016-9. Baker RC, Tiller T, Bausher JC, Bellet PS, Cotton WH, Finley AH, Lenane AM, McHenry C, Perez KK, Shapiro RA, et al.
[13] *Reviews of Infectious Diseases*, Vol 10, No 1 January-February, 1988. Charles A. Dinarello *et al.*
[14] *Reviews of Infectious Diseases* 1991; 13: 462 – 472, Norbert J. Roberts.

Pg 470:
"Accumulated direct and indirect evidence suggests an ***overall beneficial effect of physiologic temperature elevation or fever on host defense mechanisms***."

Is suppression of fever or hypothermia useful in experimental and clinical infectious diseases?[15]

Result: (antipyretic) ***adverse effects on host defense*** have modified early interest in their use as antipyretics per se…

8) QUESTION: If doctors recognize that antipyretics have an "adverse effect on host defence", on what basis does Pfizer consider that paracetamol is safe to use to reduce temperatures, if by its function paracetamol can have "adverse effects on host defence"?

Antipyretic Orders in a University Hospital[16]

Drug used: acetaminophen.

Page 31:
"antipyretics are among the most widely used pharmacologic agents. Traditional rationales for their use include relief of discomfort associated with fever, prevention of febrile seizures, avoidance of the high metabolic costs of fever in those who are malnourished or who have cardiac or pulmonary disease, and lessening of brain edema in central nervous system disease or trauma. ***However, accumulating evidence indicates that fever may be an important defense mechanism***."

"Conclusions: **Antipyretic orders are routine and correlate more strongly with hospital service than with individual patient characteristics.** They are imprecisely written and generally leave decisions about antipyretic administration to the complete discretion of the nursing staff."

9) QUESTION. If we are to consider 'best practice' to be based on the "ideal" of promoting the optimum efficiency of the biochemical and immunological functioning of patients (along with the primary medical principal of "do no harm"), why does Pfizer support routine prescription of paracetamol, without medical rationale, both in hospitals and by parents?

Page 34:
"Fever is a potentially beneficial physiologic response to infection. Experimentally induced fever has been shown to augment certain aspects of inflammation, the immune response, and antibiotic activity. Additionally, fever inhibits growth of pathogenic bacteria and enhances survival in animals with bacterial infection. Few data are available concerning the effect of fever on the outcome of human infections. **Retrospective analyses have supported a correlation between fever and an *increased* rate of survival in several studies of severe bacterial infections in humans**, but it is unclear whether fever was a cause or an effect of enhanced host defence.

10) QUESTION: Given that ***this article implies that a reduction in fever correlates with decreased rate of survival***, regardless of whether survival is "cause or effect", why would anyone wish to interfere with either "cause or effect" by prescribing antipyretics, given the preponderance of medical evidence shows ***that fever increases the patient's chances of survival***?

"What constitutes the appropriate use of antipyretics in humans remains controversial… **Antipyretics may have adverse effects of host-defense mechanisms and have been shown to prolong viral shedding in ferrets infected with influenza virus, and humans infected with rhinovirus**."

[15] *J. Infect Dis* 1970; 121: 81 – 86, Klastersky J, *et al*.
[16] *The American Journal of Medicine*, volume 88, January 1990, Stuart N. Isaacs MD *et al*.

In other words, antipyretics can make the disease worse, as is clearly stated in the next reference:

Paracetamol: use in children[17]

"**Paracetamol may prolong infection and reduce the antibody response in mild disease, and increase morbidity and mortality in severe infection**."

"there is no evidence that antipyretics prevent febrile convulsions."

"Antipyretics may be harmful."

IAS appreciates that Pfizer may consider these references out of date. However, even the World Health Organization questions the evidence for routine use of antipyretic medicines.

Bulletin of the World Health Organisation[18]

"In summary, what does the evidence seem to indicate? Fever represents a universal, ancient, and usually beneficial response to infection, and its suppression under most circumstances has few, if any, demonstrable benefits. On the other hand, some harmful effects have been shown to occur as a result of suppressing fever: in most individuals, these are slight, but when translated to millions of people, they may result in an increase in morbidity and perhaps the occurrence of occasional mortality. **It is clear, therefore, that widespread use of antipyretics should not be encouraged either in developing countries or in industrial societies**."

In other words, according to the World Health Organisation (in a reference cited 18 September 2004), the evidence seems to be all one way – in that routine use of antipyretics such as paracetamol does no significant demonstrable good, and may be harmful.

11) QUESTION: Given that it is clearly, medically stated, that PARACETAMOL when used for fever has few, if any, demonstrable benefits, can make disease worse and last longer, reduces the antibody response, increases the death rate, and may be harmful, please could Pfizer provide IAS with any medical and legally valid reason detailing why Pfizer would want to prevent IAS from informing concerned parents about this?

Paracetamol: use in children[17]

"Too many parents and health workers think that infection is bad, infection causes fever and that therefore fever is bad. In fact, fever is often a beneficial host response to infection, and moderate fever improves immunity. **Therefore it may not be a good idea to give drugs that reduce temperature to patients with several infection**. I have recently reviewed the results of 9 controlled trials in mammals of the effect of paracetamol or aspirin on mortality of virus excretions.. Four trials found that aspirin increased mortality in bacterial or viral infection. Viral shedding was increased by paracetamol or aspirin in 3 studies, possibly increased in one, and not affected in two (one used only pharyngeal washings, and one had only 9 subjects in the aspirin and placebo groups). One study found that antibody production was impaired by both paracetamol and aspirin, but no effect on antibody production was detected in the study with only 9 subjects in the aspirin and placebo groups. **This evidence suggests that aspirin and paracetamol increase mortality in severe infection, and that they may prolong the infection and reduce the antibody response in mild disease**."

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[17] *Aust Prescr* 1995; 18: 233- 234. Frank Shann, Intensive care Unit, Royal Children's Hospital, Melbourne

[18] EICHENWALD, Heinz F. Fever and antipyresis**.** *Bull World Health Organ.* http://www.scielosp.org/scielo.php?script=sci_arttext&pid=S0042-96862003000500012&lng=en&nrm=iso [online]. 2003, vol.81, no.5 [cited 18 September 2004], p.372-374. Available from World Wide Web: <http://www.scielosp.org/scielo.php?script=sci_arttext&pid=S0042-96862003000500012&lng=en&nrm=iso>. ISSN 0042-9686.)

"Conclusion: There is little evidence to support the use of paracetamol to treat fever in patients without heart or lung disease, or to prevent febrile convulsions. **Indeed paracetamol may decrease the antibody response to infection, and increase morbidity and mortality in severe infection."**

"It should be explained to parents that fever is usually a helpful response to infection, and that paracetamol should be used to reduce discomfort, but not to treat fever."

In fact, this doctor states that parents should be told **not** to use paracetamol to treat fever. It would seem that only the IAS is being "responsible" in this issue.

Other references:

"These results suggest that the systematic suppression of fever may not be useful in patients without severe cranial trauma or significant hypoxemia. Letting fever take its natural course does not seem to harm patients with systemic inflammatory response syndrome, or influence the discomfort level AND MAY SAVE COSTS." (*Arch Intern Med* 2001, Jan 8; 161 (1) 121-123)

Chickenpox treated antipyretically with Tylenol/Ibuprofen provokes bacterial skin infections into fulminant necrotising fasciitis (*Pediatr I (Pediatrics)* Vol 103, No 4, April 1999, 783-784 and 785-790) (*Infect Med* 1999 16 (5):307) Just two of many references for antipyretic induced complications of chickenpox.

"There is overwhelming evidence in favor of fever being an adaptive host response to infection... as such, it is probable that the use of antipyretic/anti-inflammatory/analgesic drugs, when they lead to suppression of the fever, result in increased morbidity and mortality during most infections; this morbidity and mortality may not be apparent to most health care workers..." *Infect Dis Clin North Am* 1996 Mar;10(1) : 1-20.)

PARENTS SHOULD ALSO BE TOLD:

Paracetamol: When, why and how much[19]

"In patients without heart and lung disease fever is harmful only at temperatures over 41°C; such high temperatures are usually caused by heat stroke or brain injury, and they do not respond to paracetamol or aspirin."

"There is no evidence that antipyretics prevent febrile convulsions."

12) QUESTION: Please could you provide IAS with the evidence that proves that Pfizer in particular, and doctors in general, conform to best practice by informing parents what constitutes the responsible use of paracetamol in children, that is, to reduce pain and discomfort, that fever is rarely harmful and **NOT TO TREAT FEVER with paracetamol;** and that paracetamol will not prevent febrile convulsion, and that paracetamol makes disease worse, increases the death rate, and may be dangerous?

To quote Pfizer's letter of 26 August, 2004, on page 3, under the heading Fair Trading Act Section 9:

"**no person shall, in trade, engage in conduct that is misleading, or deceptive, or is likely to mislead and deceive**"

According to Pfizer, Section 10 of the FT Act requires that "**no person shall, in trade, engage in conduct that is liable to mislead the public as to the nature, characteristics or suitability for a purpose of goods.**"

[19] *J. Paediatr. Child health* (1993) 29; 84 –85: Editorial

13) QUESTION: On the basis of the information above, could Pfizer please provide proof as to HOW the publication of the information IAS supplies on its website, or in this letter, would mislead the public as to the TRUE nature of paracetamol (how it alters the immune system), its characteristics (that it is harmful when used as an antipyretic) and that it serves no purpose when prescribed as an antipyretic.

14) QUESTION: Please provide proof to IAS that the information Pfizer provides to parents does NOT mislead them, as to the nature, characteristics or suitability of paracetamol to be used as an antipyretic. Please provide IAS with proof that Pfizer's information to parents neither misleads nor deceives them, by the OMISSION of vital information necessary for making an informed choice.

15) QUESTION: On the basis of question 13, and 14, please provide IAS with medical and legal justification stating why IAS may NOT state the TRUTH as presented above.

"Health Scout" and Reuters Medical News for the Professional:[20]

Findings. Those with influenza A who took antipyretics were sick much longer than their flu-infected counterparts who took nothing.

Health Scout: Quoting Dr Leland Rickman, Associate clinical professor of medicine, University of California:

"an elevated temperature may actually help the body fight the infection quicker or better than if you don't have a fever."

Quoting Dr Karen Plaisance, Associate Professor at the University of Maryland School of Pharmacy and one of the study's authors:

"Influenza A sufferers who were treated with aspirin or acetaminophen extended their illness from five days to about 8 ½ days."

16) QUESTION: Is this not further proof that paracetamol given to reduce fever during a viral infection, is unnecessary, "irrational" and dangerous, and if this is so, please explain why this is not in Pfizer's product inserts?

Risks of antipyretics in young children with fever due to infectious disease[21]

"The objective of this study was to determine whether **paracetamol** (acetaminophen) affects the outcome of children with fever due to bacterial infectious disease… **the data suggest that frequent administration of antipyretics to children with infectious disease may lead to a worsening of their illness**."

17) QUESTION: On the basis of the above information, please can Pfizer justify its demand that IAS not suggest or imply that the use of paracetamol can lead to a worsening of bacterial, or any illness, and why this information is not in Pfizer's product inserts?

Treatment of Fever[22]

"Fever is an important indicator of disease and should not be routinely suppressed by antipyretics. There is considerable evidence that fever may actually benefit the host defense mechanism.

[20] *Pharmacotherapy* December 2000; 20: 417 – 422; (http://id.medscape.com/reuters/prof/2000/12/12/04/20001201clin003.html)
[21] *Acta Paediatr Jpn* 1994 Aug; 36(4) 375 – 378. Sugimura T, et al.
[22] *Infect Dis Clin North Am* 1996, March; 10(1) : 211 – 216, Klein NC, *et al.*

…**Routine antipyretic therapy should be avoided** but may be necessary in individual patients with underlying cardiovascular or neurologic disorders."

Treatment of fever in childhood[23]

"Not all fevers need to be treated, **but many physicians do so to relieve parental concern**."

18) QUESTION: Is treating a fever with antipyretics to relieve parental concern, a legitimate medical reason, and one that Pfizer endorses as best practice by an "expert" in the medical field?

19) QUESTION: In Pfizer's advertisements on television, how does the company alert parents to the above vital information?

20) QUESTION: Please provide the IAS with copies of all Pfizer's promotional material, including that printed in medical journals, in which Pfizer states what "best practice" is, and that there is no proof of benefit from the use of paracetamol for fevers of infectious origin, except in the case of cardio or pulmonary compromise?

21) QUESTION: If Pfizer does not present these facts to either lay, or medical readers, could that omission of clinically important information be construed as being misleading or deceptive, or be likely to mislead and deceive?

HARMFUL NATURE OF PARACETAMOL.

Pfizer states **(Letter, 15 September 2004, Page 1, paragraph labeled 1, c)** that:

Pfizer demands that "IAS undertakes not to provide any information… that would tend to suggest, or imply… that paracetamol is otherwise harmful"

We refer you to the following:

Acetaminophen and the U.S. Acute Liver Failure Study Group: lowering the risks of hepatic failure[24]

"Acetaminophen overdose is the leading cause for calls to Poison Control Centers (>100,000/year) and accounts for more than 56,000 emergency room visits, 2,600 hospitalizations, and an estimated 458 deaths due to acute liver failure each year. Data from the U.S. Acute Liver Failure Study Group registry of more than **700 patients with acute liver failure across the United States implicates acetaminophen poisoning in nearly 50% of all acute liver failure in this country.** ***Available in many single or combination products, acetaminophen produces more than 1 billion US dollars in annual sales for Tylenol products alone. It is heavily marketed for its safety compared to nonsteroidal analgesics. By enabling self-diagnosis and treatment of minor aches and pains, its benefits are said by the Food and Drug Administration to outweigh its risks. It still must be asked: Is this amount of injury and death really acceptable for an over-the-counter pain reliever?"***

IAS also refers you to the New Zealand Poisons Centre, who confirmed to IAS that paracetamol is the leading cause of poisoning referred to them. When IAS asked for a citable source to back up that statement we were advised by the staff member at the Poisons Centre that it was such common knowledge as to be unnecessary to reference.

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[23] *Eur J. Pediatr* 1994, June; 153 (6) 394 – 402, Adam D, *et al.*
[24] *Hepatology.* 2004 Jul;40(1):6-9. Lee WM.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15239078

However, since you require references, we refer you to a Starship Children's Hospital document:[25]

"Paracetamol is the most common single agent involved in poisonous ingestions in young children."

IAS believes that this situation would ***not*** exist worldwide, were parents adequately provided with the information they require to make sound choices in the treatment of their children.

The current high level of poisonous ingestion primarily occurs because parents do not understand the rational and sensible use of anti-pyretics, because doctors and advertising have rigorously encouraged them in the past, to use it for a vast array of clinical situations, while at the same time, withholding the very information that shows that paracetamol used in its current routine manner as an antipyretic, is scientifically inappropriate according to the medical literature.

Furthermore, this issue of "poisoning" is of paramount concern in Spain:

Antipyretic poisoning[26]

"OBJECTIVE: To establish the current incidence of poisoning caused by oral antipyretics in the Spanish pediatric population…. The risk of acetaminophen poisoning was 5.6 higher than that of ibuprofen poisoning (RR: 5.6; 95 % CI: 4.8-6.5). Seventy three percent of poisonings occurred in children aged 1-3 years old. Poisonings were considered serious in 9.4 % of those produced by acetaminophen, 2 % of those produced by ASA and 1 % of those produced by ibuprofen…. Among the antipyretics evaluated, acetaminophen was the most frequently associated with poisoning and with severe intoxications. We recommend several preventive strategies to reduce the incidence of drug poisoning in childhood."

Common culprits in childhood poisoning: epidemiology, treatment and parental advice for prevention[27]

"Unintentional poisoning in children less than 6 years of age is a common occurrence. The majority of cases involve 1- and 2-year-old children who ingest nonpharmaceutical products. Although the clinical outcomes of these exposures is usually favourable, deaths do occur…. The exposures most commonly reported by the AAPCC TESS are cosmetic/personal care products (e.g. perfume, cologne and aftershave), household cleaning substances (e.g. bleach and alkaline corrosives) **and analgesics [e.g. paracetamol (acetaminophen)].** Prevention is important and exposure to poisons should be considered a preventable childhood injury. The use of child-resistant packaging and the secure storage of household substances are the basis of preventing unintentional exposures. Parents and healthcare professionals need to be aware of what constitutes high risk exposure, as well as those exposures which are common but not serious. Poison prevention efforts should also address the appropriate role of the poison information centre."

And Norway:

Paracetamol poisonings in Norway 1990-2001[28]

"The number of paracetamol poisonings has increased since 1990 in accordance with the dramatic increase in sales of paracetamol in Norway. Although the mortality of paracetamol poisoning is low (1-2 deaths annually), it represents the most critical poisoning problem among non-opioid analgesics. It is important to monitor the morbidity and mortality of paracetamol poisoning, as new regulations

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[25] http://www.starship.org.nz/docs/paracetamol.pdf.

[26] *An Esp Pediatr.* 2002 Apr;56(4):318-23.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11927099

[27] *Paediatr Drugs.* 1999 Oct-Dec;1(4):313-24.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10935429&dopt=Abstract

[28] *Tidsskr Nor Laegeforen.* 2004 Jun 17;124(12):1624-8. Boe GH *et al.*
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15229706

introduced from 2003 will increase the availability of paracetamol and other selected non-opioid analgesics."

Furthermore if the USA considers parents should be advised of liver toxicity, why should not New Zealand parents be provided with the following information?

Therapeutic misadventures with acetaminophen: hepatoxicity after multiple doses in children[29]

"We compiled reports of acetaminophen hepatotoxicity after multiple overdoses from published cases… Serum acetaminophen levels for which an estimate of time from last dose could be calculated were available for 30 patients, of which 22 levels were greater than the toxic range described for acute ingestion. Twenty-four of 43 patients (55%) died, with an additional three surviving after orthotopic liver transplantation. **Parents should be advised about the potential hepatotoxicity of acetaminophen when given to ill children in doses exceeding weight-based recommendations."**

That liver toxicity can have serious ramification is without doubt. That dose miscalculations by parents because of lack of education is a factor, is also without doubt:

Outcome of acetaminophen overdose in pediatric patients and factors contributing to hepatotoxicity[30]

"Seventy-three medical records of pediatric patients admitted for acetaminophen overdose were reviewed. Twenty-eight patients (39%) had severe liver toxic effects, and six of them underwent liver transplantation. ***Multiple miscalculated overdoses given by parents***, with delay in therapy, are risk factors and the major cause of overdose in children 10 years of age or younger."

The inappropriate routine use of paracetamol as an antipyretic, and the continued high rate of paracetamol poisoning in New Zealand (and increases in poisonings world wide), indicate to the IAS a continued failure of the medical profession and manufacturers of paracetamol and paracetamol containing medications to diligently promote known best practice in both advertising and clinical advice regarding the use of paracetamol.

Further, it suggests that current unrestricted availability over the counter paracetamol containing medications, without medical oversight, continues to have serious ramifications for the health of babies in New Zealand and world wide.

Treatment of fever in childhood[31]

"The most commonly used antipyretic drugs are acetylsalicylic acid (ASA), paracetamol (acetaminophen) and dipyrone (metamizol). …**Paracetamol is the most common cause of acute hepatic failure**… in the light of these findings, the extensive use of antipyretics drugs has been seriously questioned."

Page 398:
"**Paracetamol has a pronounced liver toxicity**. In the **United Kingdom paracetamol is considered to be responsible for more cases of acute hepatic failure than any other cause.**"

Page 399
"the potential for toxicity of ASA and paracetamol, the two most extensively used antipyretics in the febrile child, underlines the constraints within which treatment decisions have to be made. **The fact**

[29] *J Pediatr*. 1998 Jan;132(1):22-7. Heubi JE, Barbacci MB, Zimmerman HJ.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9469995
[30] *J Pediatr*. 1997 Feb;130(2):300-4.Rivera-Penera T, *et al.*
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9042136
[31] *Eur J. Pediatr* 1994, June; 153 (6) 394 – 402 Adam D, et al

that both drugs are sold as "over the counter" products, while the medication of child fever often occurs without medical control, *should be a matter of concern*.

"The statistics on poisonings with these drugs as established in the United Kingdom and the USA are impressive and ***the scope of the problem calls for urgent solutions***."

Pfizer may suggest that the majority of patients admitted with acute liver toxicity have no long terms sequelae. However, IAS disputes this:

There are many articles in which "acetaminophen intoxication with therapeutic intent" occur. They are well summarized in two letters in the *Journal of Pediatrics*, November 1998, volume 133, No 5, Pages 712 – 714.

In the second letter, Dr Gregory L. Kearns outlines detailed descriptions of what he considers should be the very strict criteria laid down by clinicians, by which parents are allowed to treat their own children. This involves clearly WRITTEN directions to parents detailing the risks and benefits, the need for proper doses, and how they are calibrated, the use of other non-pharmacological measures to reduce temperature and most importantly:

"Finally, the duration of antipyretic use in every instance should be limited to enable the effective diagnoses of serious illnesses that may be heralded by the production of fever. It is clear that the regular application of rational guidelines for the provision of antipyretic therapy to paediatric patients can only benefit the routine care of infants and children. If done religiously, acetaminophen intoxication with therapeutic intent will become the victim of phamacologic extinction"

IAS also points out that parents are rarely told these facts:

Paracetamol[32]

"Since the toxic level of paracetamol is not much greater than its therapeutic level patients must be cautioned not to exceed the recommended dose. They should be warned that cold remedies may contain paracetamol and/or aspirin, and inadvertent overdose is possible."

Risk factors for toxicity [33]

"The toxic dose of acetaminophen is highly variable. In adults, single doses above 10 grams or 140 mg/kg have a reasonable likelihood of causing toxicity. In adults, single doses of more than 25 grams have a high risk of lethality. Toxicity can also occur when multiple smaller doses within 24 hours exceeds these levels, or even with chronic ingestion of smaller doses. However, unintentional acetaminophen overdose in children rarely causes illness or death. This may be due in part to the immature cytochrome P450 enzyme system in children.

Some individuals are more susceptible to hepatotoxicity, with toxic doses as low as 4 g/day, and death with as little as 6 g/day."

And as WHO says in another pdf in 2003:[34]

"Growing evidence shows the potential for hepatotoxicity in children given multiple therapeutic or subtherapeutic doses of acetaminophen (paracetamol). Product information recommends a maximum daily dose of 60 mg/kg, but it is not uncommon for children to receive 90 mg/kg/day in hospital."

How is this affected when……

[32] http://www.ntmedic.com.au/Front%20Page/Aug%2004%20Chronicle.htm
[33] http://www.webster-dictionary.org/definition/acetaminophen
[34] *Reference:* RUSSELL, Fiona M., SHANN, Frank, CURTIS, Nigel *et al*. Evidence on the use of paracetamol in febrile children. *Bull World Health Organ*, 2003, vol.81, no.5, p.367-372. ISSN 0042-9686 Available at: *http://www.scielosp.org/scielo.php?script=sci_pdf&pid=S0042-96862003000500011&lng=en&nrm=iso&tlng=en*

Outcome of acetaminophen overdose in pediatric patients and factors contributing to hepatotoxicity[35]

Page 302:
"concomitant viral infections, metabolic problems or fasting can potentially aggravate hepatic toxic effects. The majority of patients who ingested multiple overdoses had fever as an indication for taking the antipyretic agent and thus may have been harboring an underlying condition."

Therapeutic misadventures with acetaminophen: Hepatotoxicity after multiple doses in children[36]

Page 26:
"In most multiple accidental overdoses, infants and children are febrile and acutely malnourished…. Concern may be raised because several subjects received reported doses that were only slightly above the recommended doses… If the reported doses are accurate, our findings suggest that the therapeutic index for acetaminophen may be 1 to 1.7 when an ill, febrile child received acetaminophen. In addition, Alonso *et al* suggest that even therapeutic doses of acetaminophen may lead to centrilobular necrosis in the susceptible child."

Which all calls into question again, the unnecessary use of acetaminophen/paracetamol as an antipyretic when it has no proven benefit, a condition which can of itself provoke toxicity conditions.

Further: "Whatever the true frequency of acetaminophen-associated hepatotoxicity from multiple accidental overdoses in children, it is import for physicians to take a proactive role in advising parents on the safe use of this drug and other over-the-counter preparations. As a portion of anticipatory guidance, physicians should discuss fever management and the judicious use of antipyretics. This discussion should include appropriate weight-based dosing schedules, the use of sponge bathing if fever is unresponsive, ***and the potential risks of excess acetaminophen when given to the sick, acutely malnourished child***."[36]

22) QUESTION: Could it also be argued that if IAS agreed to Pfizer's demands to never suggest or imply that paracetamol is (otherwise) harmful, detrimental, or might worsen disease or cause death, that IAS might be accused in the future of acting in concert with manufacturers providing information which could mislead and deceive parents as to the true nature of paracetamol, by withholding known, published medical FACTS?

23) QUESTION: Given that today, paracetamol poisoning is the leading cause of admission for inadvertent poisoning, according to Starship and the Poisons Centre, and given that the above information clearly portrays the demonstrable harm of paracetamol (which all parents have a right to know about under "informed consent" provisions, and which anyone has a right to provide), please provide to the IAS, in writing, all relevant law proving that Pfizer's demands of IAS are legitimate.

24) QUESTION: Please provide IAS with the documented evidence that shows that, in order for Pfizer NOT to deceive and mislead parents, that Pfizer does, in fact, provide parents with all the evidence discussed above, that is, that paracetamol can cause acute poisoning, and is therefore potentially harmful.

(IAS does not wish to read vague phrases such as "do not exceed stated dose". That tells parents nothing)

[35] *Journal of Pediatrics* February 1997, volume 130 Number 2 Teresa Rivera-Panera MD. *et al*
[36] *The Journal of Pediatrics* January 1998, Volume 132, Number 1, James E. Heubit, MD, *et al.*

INFORMATION: STANDARD OF CARE.

In Pfizer's letter to IAS dated 26 August 2004, Pfizer states on page 3, bottom paragraph the following:

"The IAS Representations are negligent…

IAS has not met the standards of care that would be expected of an expert in the medical field."

Apart from the fact that IAS has never represented itself as being "expert" in the medical field, we would ask the following:

25) QUESTION. Given that IAS "represented" published, referenced evidence as to the very real potential immunological and safety hazards of paracetamol to the children of this country, and, contrary to Dr Baker's assertion, we did not misinterpret the information in the article, we would ask Pfizer to present IAS with the evidentiary proof as to:

a) in what way the IAS information is negligent, and in what way it does not meet standards of care… and

b) how it is that Pfizer, who appears not to inform parents of any the clinical issues relating to "harm" that IAS raise, can consider that they, Pfizer, meet the standard of care that would be expected from an expert in the medical field.

MONETARY LOSS, LOSS OF GOOD WILL OR REPUTATION.

Further, Pfizer alleges in the letter dated 26 August, 2004, page 3, third to last paragraph, that IAS representations *"are likely to cause Pfizer monetary loss as well as loss or reputation and goodwill."*

The IAS agrees that should our accurately referenced medical representations result in parents no longer using paracetamol and/or paracetamol containing medications as an antipyretic, sales of paracetamol containing medications may well fall. We agree this may "hit" Pfizer in the wallet.

But IAS would welcome the enhancement of the health and wellbeing of those children, who, by avoiding unnecessary paracetamol containing medications through their parents finally being "educated", will reduce their chances of atopy, asthma (see later), immune suppression, illness prolongation, severity and other possibilities of "harm".

IAS would like to think that Pfizer, likewise, would consider that these benefits would outweigh any financial loss to their company.

Pfizer also object in the letter dated 15 September 2004, page 2, to the comments made in the paracetamol pdf that:

"their own literature has given enough warning to totally change the face of care of children with fevers, yet THEY HAVE DONE NOTHING to try and change parents perceptions on fever or the use of paracetamol/acetaminophen. And why is that? Follow the money. Over the counter antipyretics are the best money spinner there is. Wall Street Rules. Again."

The *Hepatology*, 2004, extract below, is pertinent, since Dr Lee officially infers exactly what IAS does, when he says:

"Available in many single or combination products, **acetaminophen produces more than 1 billion US dollars in annual sales for Tylenol products alone**. It is heavily marketed for its safety

compared to nonsteroidal analgesics. By enabling self-diagnosis and treatment of minor aches and pains, its benefits are said by the Food and Drug Administration to outweigh its risks. It still must be asked: **Is this amount of injury and death really acceptable for an over-the-counter pain reliever**?"[24]

26) QUESTION: Dr Lee infers that the silence regarding the detrimental effects of acetaminophen/paracetamol may well be related to a certain sum of money. Please explain why it is acceptable to Pfizer for someone like him to say this, and why is it unacceptable for IAS to ask the same questions or to draw the same inferences?

"Acetaminophen overdose causes more than 450 deaths due to acute liver failure each year in the United States and this number appears to be on the rise. In 2001, the U.S. Acute Liver Failure (ALF) Study found acetaminophen responsible for 39 percent of cases. In 2003, the number had risen to 49 percent.

More than 50 percent of the country's cases of acute liver failure are related to acetaminophen, according to the ALF Study, reports Lee."[37]

"Indications for liver transplantation include chronic liver failure (eg, cirrhosis), acute liver failure (eg, acetaminophen toxicity), metabolic liver disease (eg, inborn errors of metabolism), and primary liver tumors."[38]

27) QUESTION: Please explain how all these deaths, liver transplants and renal transplants enhance the goodwill and reputation of any firm providing paracetamol and/or paracetamol containing medications, and how the attempted suppression of this information by Pfizer, will assist Pfizer in anyway, in terms of goodwill and reputation.

It is the contention of the IAS that the goodwill and reputation of companies manufacturing products containing acetaminophen/paracetamol, would have been materially enhanced had Pfizer/Johnson & Johnson been prepared to provide all the information to parents, and not pre-emptively try to prevent any "body", IAS or FDA, from saying what should have been said in the first place, by the drug manufacturers.

RE-EDUCATION OF PARENTS.

Further, Pfizer, and any other company that manufactures products containing acetaminophen/paracetamol, must have been aware of medically documented concerns such as these, ***which could be argued to be the direct result of company "advertising"***:

Parental Fever phobia and its correlates[39]

"It is concluded that ***undue fear and overly aggressive treatment of fever are epidemic*** among parents of infants and young children, even among the highly educated and well-to-do. ***Considerable effort will be required on the part of pediatricians and other child health workers to re-educate these parents*** about the definition, consequences, and appropriate treatment of fevers."

28) QUESTION: Who has been the primary educator and conditioner of parents for all these years? Why do parents now have undue fear of fevers? Who has provided the promotional information that tells parents it is okay for fevers to be treated routinely with paracetamol based products?

[37] http://www.medicalnewstoday.com/medicalnews.php?newsid=11017
[38] http://www.emedicine.com/emerg/topic605.htm
[39] *Pediatrics* 1985, June 75 (6) 1110 – 1113. Kramer MS et al.

RISK FACTORS INVOLVED IN BACTERIAL MENINGITIS.

Pfizer demands that IAS not provide any information which would tend to suggest or imply that Pamol® or any other medication containing paracetamol is associated with the development of meningococcal disease.

IAS finds it very hard to get past the quotes from the medical literature:

With regard to the Media release you enclosed with your letter dated 26th August 2004, in which the primary author Michael Baker was quoted as saying:

"In the study, analgesic use itself was not attributed as a cause of meningococcal disease and Pamol was not even mentioned…"

Firstly, the IAS never said "Pamol®" was a "cause" of meningitis, but clearly quoted the exact phrase from the article which clearly stated that anti-pyretics could not be ruled out as a "risk" factor, … which is consistent with all the other medical evidence presented in this letter. Here are ALL the quotes from Dr Baker's article:

Household crowding a major risk factor for epidemic meningococcal disease in Auckland children[40]

Page 988.
"***analgesic use*** **and** attending substantial social gatherings were also still ***strongly associated with the risk*** of contracting the disease."

Page 989:
"Although ***we have interpreted analgesia use to be an indicator of recent illness***, **we cannot exclude the possibility that acetaminophen use itself is a risk factor for meningococcal disease**."

29) QUESTION. Is Dr Baker now saying that he didn't mean to write this after all?

The meaning in the article is perfectly clear. It is only Dr Baker and Pfizer who now state that IAS said that paracetamol was a "cause".

Page 987:
"Analgesic use was defined as analgesics taken in the past 2 weeks, excluding, for cases, those taken for identified early symptoms of meningococcal disease. **These analgesics were predominantly acetaminophen products**… because analgesics showed a stronger relationship with meningococcal disease, the use of analgesics may be a better measure of more severe illness than reported individual symptoms."

With regard to the Media release you enclosed with your letter dated 26th August 2004, in which the primary author Michael Baker was quoted as saying:

"In the study, analgesic use itself was not attributed as a cause of meningococcal disease and ***Pamol was not even mentioned***…"

IAS has never said it was a cause. There is a distinction between a 'cause' and a 'risk factor'.

30) QUESTION: While Dr Baker never mentioned Pamol® in the article, exactly what form of paracetamol/acetaminophen do most New Zealand parents administer to their children?

[40] *Pediatric Infectious Disease Journal*, volume 19, No 10, October 2000; 19: 990 - 995. Michael Baker et al.

Therefore, in IAS's opinion, Dr Baker's statement that he never mentioned "Pamol" in the article, while legally accurate, is "generically" disingenuous, since most children are administered acetaminophen/paracetamol as an elixir or syrup, ie. Pamol®.

Michael Baker continued to deliberately mislead, by saying that our claims are "inaccurate and ***could mislead parents who may want to appropriately use a proven safe medication to reduce pain and fever in children with mild infection.***"

It would have been beneficial if Dr Baker had got the IAS "claims" right in the first place.

The issue of acetaminophen/paracetamol in children with a bacterial meningitis again raises the questions previously asked of Pfizer. But, in case these questions have not been answered, here they are again:

31) QUESTION: Is paracetamol a *proven safe* medication that it is *"appropriate"* to use routinely for fever in normal children with mild infection which might progress to serious infection?

32) QUESTION: "When does a parent KNOW when a mild infection may become serious, particularly when doctors have difficulty in this area?"

Dr Baker lumps pain in with fever. He is mistaken.

Fever revisited[41]

"**However there are no data that show that fever by itself is painful… no pain is associated with these increases in body temperature**."

(Other articles support this, **therefore, Dr Baker's comment linking pain with fever is both unscientific and irrelevant**.)

Furthermore, the evidence regarding suppression of fever increasing disease severity and mortality in bacterial illnesses is more extensive than Dr Baker has alerted you to:

Spontaneous bacterial peritonitis[42]

"Temperature ***greater than 38***°C was associated with **increased survival** in spontaneous bacterial peritonitis."

33) QUESTION: Outside of those with heart or lung conditions, why would Pfizer want anyone to be more likely to die by keeping a temperature down, particularly if it was caused by a product sold by themselves?

Polymicrobial sepsis: an analysis of 184 cases using log linear models[43]

Result: An increase in mortality with ***absence of fever*** in polymicrobial sepsis.

Rhetorical…. QUESTION: Why then, would anyone want to jeopardize survival by keeping a temperature down?

[41] *Pediatrics* vol 90, No 6, December 1992 Matthew J. Kluger page 859
[42] *Am J Med*, 1978; 64: 592 – 298 Weinstein MP et al.
[43] *Am J Med Sci*, 1980: 280; 73 – 80, Mackowiak P A et al.

Factors affecting mortality of Gram negative rod bacteremia[44]

and

Gram-negative bacteremia IV: re-evaluation of clinical features and treatment in 612 patients[45]

Result. An increase in mortality with ***absence of fever*** in gram-negative bacteremia.

Rhetorical…. QUESTION: Why then, would anyone want to jeopardize survival by keeping a temperature down?

Pneumococcal meningitis at Harlem hospital[46]

Result: An increase in mortality with ***absence of fever*** in pneumococcal meningitis.

Rhetorical…. QUESTION: Why then, would anyone want to jeopardize survival by keeping a temperature down?

All of these sources, including *Aust Prescr* 1995; 18: 233- 234 (page 10). state that reduction of temperature is associated with increased mortality and morbidity, in all forms of bacterial meningitis, and viral diseases.

Therefore on the basis of proven, referenced facts above, not only does IAS disagree with Pfizer's, and Michael Baker's inference that paracetamol, or any antipyretic, can be safely administered for any mild illness involving fever (particularly if that mild infection later turns out, as per his study, to turn into serious bacterial meningitis), we also agree with the stated quote in his own article, and reinforced from Australia and elsewhere in the world, that "paracetamol" used as an antipyretic, is a risk factor which can, and does increase the severity of infection, and mortality, in all forms of bacterial meningitis.

34) QUESTION: Please provide us with all the documentation showing that Pfizer's demands that the IAS stop telling the truth as outlined above, that paracetamol has the potential to increase both severity and mortality in any infectious disease, are morally, medically, ethically and legally valid.

PARACETAMOL'S RELATIONSHIP WITH ATOPY AND ASTHMA.

Further, IAS believes that parents also have the right to make informed decisions, to be informed of and to understand other dangers that paracetamol and paracetamol containing medications may present to their children such as the following:

Paracetamol sales and atopic disease in children and adults: an ecological analysis[47]

"The authors recently observed that frequent paracetamol use was positively associated with asthma and rhinitis in young adults. ….Their associations with national 1994/1995 per capita paracetamol sales were measured using linear regression. Paracetamol sales were high in English-speaking countries, and were positively associated with asthma symptoms, eczema and allergic rhinoconjunctivitis in 13-14-yr-olds, and with wheeze, diagnosed asthma, rhinitis and bronchial

[44] *Arch Intern Med.* 1971: 127: 120 – 128. Bryant R. E et al.
[45] *Am J. Med*, 1980; 68: 344 – 355. Kreger, B. E. et al.
[46] *N Y State J Med.* 1971; 71: 2747 – 2754. Richter R W et al.
[47] *Eur Respir J.* 2000 Nov;16(5):817-23. Newson RB, Shaheen SO, Chinn S, Burney PG
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=retrieve&db=pubmed&list_uids=11153577&dopt=Abstract

responsiveness in adults. The prevalence of wheeze increased by 0.52% in 13-14-yr-olds and by 0.26% in adults ($p<0.0005$) for each gram increase in per capita paracetamol sales. These ecological findings require cautious interpretation, but raise the possibility that variation in paracetamol usage may explain some of the variation in atopic disease prevalence between countries."

As would be expected with atopy, this article looking at asthma deserved further consideration particularly for parents with asthmatic children:

Asthma morbidity after the short-term use of ibuprofen in children[48]

"However, the risk of an outpatient visit for asthma was significantly lower in the ibuprofen group; compared with children who were randomized to acetaminophen, the relative risk for children who were assigned to ibuprofen was 0.56 (95% confidence interval: 0.34-0.95). CONCLUSIONS: Rather than supporting the hypothesis that ibuprofen increases asthma morbidity among children who are not known to be sensitive to aspirin or other nonsteroidal antiinflammatory drugs, these data suggest that **compared with acetaminophen, ibuprofen may reduce such risks**. Whether the observed difference in morbidity according to treatment group is attributable to increased risk after acetaminophen use or a decrease after ibuprofen cannot be determined."

IAS would also refer Pfizer to the *New Zealand Herald*, Monday September 10, 2001, in which a Swedish study, discussed in the *European Respiratory Journal* of the previous week, was discussed in detail. It demonstrated a possible paracetamol-asthma link, and also stated that aspirin could cause serious attacks in a small number of sufferers***. It quoted the Asthma and Respiratory Foundation, as having warned people with asthma to avoid taking large doses of paracetamol frequently.***

We note with interest, that on page three in the *New Zealand Herald*, Friday 17 September, the finding that giving children antibiotics or paracetamol early in life may increase their risk of asthma, was confirmed.

What this underscores to the IAS, is that paracetamol has a noticeable down regulation of the immune system in more ways than just preventing the immune system from fully and efficiently dealing with infection processes.

Yet very few parents are warned, or know, that asthmatic children require special care with regard to paracetamol.

IAS sees no reason to **not** continue to refer parents to the medical literature; medical literature that shows that to suppress any fever of infectious origin with any antipyretic using the current medical practice and advertising standards in this country, has the potential to increase the seriousness of any infectious disease, including bacterial sepsis of any kind, and that acetaminophen/paracetamol products are shown to have the potential to damage the health and welfare of children through suppression of the immune system, and acute poisoning.

IAS does NOT accept that these representations would contravene Sections 9 and 10 of the Fair Trading Act.

Further, if the implementation of "best practice" were to result in a substantial decrease in the use of any paracetamol containing product, manufactured by any pharmaceutical company in this country, IAS would NOT consider that would result in loss of reputation and goodwill to any such company.

IAS considers that such an action would materially contribute to the improving the health and welfare of all such children no longer routinely or automatically given any antipyretic drug of unproven benefit.

[48] *Pediatrics.* 2002 Feb;109(2):E20
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11826230

IAS considers the referenced information provided in this letter to be neither negligent, false, nor misleading in any way, and that the information provided in this letter conforms to the highest standard of social responsibility for the ultimate concern of the health and welfare of potential paracetamol recipients.

Were any manufacturing company to provide such information on paracetamol/ acetaminophen products to parents, we consider that the provision of that information would materially **increase the reputation and goodwill of the "provider"** by demonstrating honesty and "caring" for the health and well being of the recipients of any such product.

In Pfizer's letter dated 26 August 2004 letter on page 4, you state that:

"The IAS Advertisements contravene the Advertising Standards Authority Code for Therapeutic Advertising… and that…

"Advertisements should observe a high standard of social responsibility as consumers rely on therapeutic products and services for their health and well being."

Referring to Pfizer's comments (on the same page) that:

"Advertisement should not by implication, omission, ambiguity of exaggerated claim, mislead or deceive, or be likely to mislead or deceive consumers, abuse the trust of or exploit the lack of knowledge of consumers, exploit the superstitious or without justifiable reason, play on fear,"

IAS invites Pfizer, if they continue to feel this way about what we say about paracetamol, now or in the future, to make a formal complaint to the Advertising Standards Authority.

The IAS considers that were we to give any ***less*** information to fellow parents (than that which we have provided to Pfizer in this letter), **such a failure would mislead and deceive those seeking to be fully informed on the issue and** would abuse their trust, and lack of knowledge, that the information we supplied about paracetamol/acetaminophen products was complete.

IAS therefore consider the information in this letter to be of the highest medical integrity possible, as we have not failed to report known facts with definable serious implications necessary to make an informed choice.

If you disagree that we can legitimately continue to inform anyone using:

1) the factual basis of referenced medical journal articles quoted in this letter, or wherever else we find referenced medical information;

2) our continued legitimate use of the non-proprietary term "paracetamol", which is not registered to Pfizer, or any other pharmaceutical company….

3) or the clinical standards or implications behind the medical information provided,

please provide us with all the legal and medical information to prove otherwise.

IAS asks that Pfizer ensures that they have the answers to our questions returned to us ***by 5.00 p.m., Wednesday, 29th September, 2004.***

Yours sincerely

The Executive Committee of
The Immunisation Awareness Society