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### The Importance of Human Data in the Establishment of Occupational Exposure Limits

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## The Importance of Human Data in the Establishment of Occupational Exposure Limits

Edward V. Sargent,<sup>1,\*</sup> Bruce D. Naumann,<sup>1</sup> David G. Dolan,<sup>1</sup> Ellen C. Faria,<sup>1</sup> and Lisa Schulman<sup>2,3</sup>

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### ABSTRACT

The use of animal vs. human data for the purposes of establishing human risk was examined for four pharmaceutical compounds: acetylsalicylic acid, cyclophosphamide, indomethacin and clofibrac acid. Literature searches were conducted to identify preclinical and clinical data useful for the derivation of acceptable daily intakes (ADIs) from which a number of risk values including occupational exposure limits (OELs) could be calculated. OELs were calculated using human data and then again using animal data exclusively. For two compounds, ASA and clofibrac acid use of animal data alone led to higher OELs (not health protective), while for indomethacin and cyclophosphamide use of animal data resulted in the same or lower OELs based on human data alone. In each case arguments were made for why the use of human data was preferred. The results of the analysis support a basic principle of risk assessment that all available data be considered.

**Key Words:** human data, risk assessment, occupational exposure limits.

### INTRODUCTION

The science of toxicology is based on the assumption that animal tests are useful to predict the adverse effects of chemicals in humans. This is especially important for pharmaceuticals where the preclinical assessment in animals is used to determine whether it is safe to administer the compounds to humans clinically. Because of this there is a relatively rich database of both animal and human data for most human pharmaceutical compounds. There have been surprisingly few attempts, however, to use the data sets to assess the correlations between effects in animals and humans (Lumley 1990; Igarashi 1994). A recent report of the outcome of a 1999 ILSI workshop examined the concordance of the toxicity of pharmaceuticals in

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animals and humans (Olson *et al.* 2000) and Dourson *et al.* (2001) performed an extensive evaluation of the basis for reference doses (RfDs) and reference concentrations (RfCs). In both studies, the conclusion was that both human and animal data should be used in order to derive scientifically appropriate and health protection risk estimates.

While the requirements for performing animal and human tests are relatively well defined for pharmaceuticals and pesticides, they are much less so for other types of chemicals. For many chemicals, hazard determinations are based primarily on animal data. Human epidemiologic data are either descriptive (hypothesis generating) or analytic (designed to evaluate hypothesized causal association). Typically, even the analytic studies lack sufficient exposure information or statistical power to detect and attribute responses to allow dose-response analysis. Thus, risk assessments are for the most part based on animal data.

Recent attention has been focused on the use of human data for making a variety of regulatory decisions from pesticide registrations to calculating RfDs to the classification and labeling of hazardous chemicals. Of particular concern are the ethical issues surrounding human testing (McConnell 2000) and the establishment of precedence for human data over animal data (or vice versa). It is the latter issue that we have considered in this paper. Over the last 20 years we have established 150 occupational exposure limits for pharmaceutical active ingredients for which there was a full preclinical and clinical data set. For each of those compounds the entire set of data was reviewed, however the OEL was based in each case on a human clinical endpoint. In this paper we reviewed the published animal and human data for four pharmaceutical compounds: acetylsalicylic acid, cyclophosphamide, indomethacin and clofibrac acid. The data were used to derive acceptable daily intakes (ADIs) from which any number of risk values such as Ambient Water Quality Criteria (AWQC), occupational exposure limits (OELs) or risk reference doses (RfDs) could be calculated. In this paper, we specifically evaluated the impact of having both animal and human data on the derivation of an OEL for each compound. The compounds were selected however for use in an evaluation of environmental risk. Specific exposure data were available for each of these four compounds (Schulman *et al.* 2002). The hazard evaluations and dose-response assessments completed for that study were used in the present evaluation. The animal and human data available for all four compounds were summarized in a case study fashion. For each compound the basis for derivation of the OEL is also provided.

### ACETYLSALICYLIC ACID

Acetylsalicylic acid (ASA) or aspirin is a human and veterinary over-the-counter medicine that is used as an anti-inflammatory, analgesic, antipyretic and anticoagulating agent. The majority of information in the published literature in both humans and animals is from the oral route, however, salicylates are known to be absorbed through intact skin.

#### Animal Data

ASA is not acutely toxic by the oral route in animal studies with reported LD50s of 1.5 and 1.1 g/kg in rats and mice, respectively. In animal toxicity studies,

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significant species variability in response to ASA has been shown due to different rates of metabolism. ASA is negative in a series of mutagenicity assays (Jasiewicz and Richardson 1987; HSDB 2001) and, when given to rats in the diet at 0.5% for 68 weeks, was not carcinogenic.

ASA is maternotoxic, embryofetotoxic, and teratogenic in animal studies. Teratogenicity has been demonstrated in rats (Beall and Klein 1977; Davis *et al.* 1996) and mice (Trasler 1965). Teratogenicity is thought to be due to the metabolic hydrolysis product, salicylic acid (Kimmel *et al.* 1971). The lowest LOAEL for teratogenicity was shown to be 10 mg/kg/day for 2 to 3 days. This dose given to rats orally on days 19 to 21 of gestation caused a delay in parturition and increased fetal deaths (Waltman *et al.* 1973). ASA also causes constriction of the ductus arteriosus in fetal rats (LOAEL = 14 mg/kg) and lambs (LOAEL = 55 mg/kg) (Momma and Takao 1990; Heyman and Rudolph 1976).

### Human Data

In humans, ASA is known to cause skin, eye, and upper respiratory tract irritation after direct contact and gastrointestinal bleeding following chronic ingestion. ASA is a known systemic and respiratory allergen and can produce anaphylaxis at doses in the lowest end of the therapeutic range in sensitized individuals. Significant toxicity may result from single oral doses above 300 to 500 mg/kg and doses as low as 10 to 30 grams have caused fatalities in adults and as little as 5 grams has caused fatalities in children (HSDB 2001). There is no evidence that ASA is a human carcinogen and it may actually afford protection from some cancers (Garcia-Rodriguez and Huerta-Alvarez 2001).

Approximately 80 to 100% of an oral dose of ASA is absorbed. Following oral administration, ASA is nearly completely (99%) hydrolyzed to salicylic acid either in the gastric mucosa or by tissue esterases. Salicylic acid and other salicylate metabolites such as salicyluric acid, phenolic salicylate, acyl glucuronides and gentisic acid are excreted in the urine. The plasma half-life is 15 to 20 minutes.

ASA exerts antiinflammatory and antipyretic effects by the inhibition of the enzyme cyclooxygenase 2 (COX-2) and subsequently by the inhibition of prostaglandin production. Both isoforms of COX, 1 and 2, are inhibited by ASA and the inhibition of COX-1 is largely responsible for the gastrointestinal irritation, bleeding, and ulcers associated with ASA use. ASA also inhibits platelet aggregation through inhibition of thromboxane A<sub>2</sub> and prostacyclin and, therefore, is useful as an anticoagulant and for the prevention of thrombosis. Typical chronic therapeutic doses of ASA vary depending on the condition treated. The highest doses are used for the treatment of rheumatic diseases (5000 to 6000 mg/day). The lowest doses are used for anticoagulant therapy (30 to 150 mg/day). For post-surgical prevention of thrombosis and prevention of myocardial infarction, the typical dose range is 75 to 325 mg/day. Treatment for pain ranges from 650 to 1300 mg/day (AHFS 2000). Other effects, including a 50% reduction in risk of colorectal cancer at 300 mg/day and an increased risk of GI bleeding at 325 mg/day (Kelly and Kaufman 1996), have also been seen.

Aspirin is commonly consumed during pregnancy and does not appear to be a human teratogen (Reprotox 2001). ASA has been given for the prophylactic treat-

ment of pre-eclampsia at doses ranging from 60 to 150 mg/day (AHFS 2000). No adverse effects were seen at 18 months in children of mothers taking 60 mg/day for preeclampsia (Farrell *et al.* 1995). At that dose there was no effect on the circulation of fetuses and newborns. Epidemiology studies confirm that aspirin given within the therapeutic range has not caused an increase in birth defects. Exact doses given were not provided in these studies however. ASA has been given therapeutically to newborns for treatment of patent ductus arteriosus with 60 mg/kg in 4 equal doses over 6 hours being minimally effective (van Overmeire *et al.* 1995).

#### Derivation of an OEL for ASA

The current ACGIH Threshold Limit Value (TLV) (originally adopted in 1980) and OSHA Permissible Exposure Limit (PEL) for ASA is 5 mg/m<sup>3</sup> as an 8-hour time-weighted average. This was deemed low enough to prevent workers from experiencing effects on clotting time and platelet aggregation as well as gastric and respiratory irritation, although supporting dose-response data in the documentation suggesting a low clinical dose of 150 mg/day are dated (ACGIH 1996). This TLV/PEL would translate into an acceptable daily intake (ADI) of 50 mg assuming the average worker breathes 10 m<sup>3</sup> in an 8-hour workday. After examining the most current animal and human dose response data, it would appear that the current lowest-observed effect level (LOEL) for anticoagulation therapy of 30 mg/day would be the most appropriate dose for establishing an OEL. From this an ADI of 1 mg/day is established assuming an uncertainty factor of 3 to account for the use of a LOEL (UF<sub>L</sub>) to estimate a NOEL and 10 for interindividual variability (UF<sub>H</sub>). This ADI is well below the therapeutic dose used to treat pre-eclampsia and the dose at which no maternotoxic or fetotoxic effects are seen. This ADI would translate into an OEL of 0.1 mg/m<sup>3</sup> given in Table 1. Ignoring the human data and examining only the available animal data, the critical endpoint continues to be maternotoxic and fetotoxic effects from a rat study showing parturition delay, increased bleeding and fetal death. Using the LOEL of 10 mg/kg, an OEL of 0.3 mg/m<sup>3</sup> as an 8-hour TWA is derived, incorporating uncertainty factors of 3 for LOEL to NOEL, 6 for animal to human based on allometric scaling and 10 for interindividual variability.

#### CYCLOPHOSPHAMIDE

Cyclophosphamide is a polyfunctional alkylating agent that has been used to treat a variety of cancers and other medical conditions since the late 1950s (Chabner *et al.* 1996). There is a wealth of published literature on its utility as an antineoplastic agent and the adverse effects associated with therapeutic use, including the secondary malignancies observed following initial cancer therapy. A significant number of studies have also been published on the effects of cyclophosphamide in animals, particularly in the areas of reproductive and developmental toxicity (McClure *et al.* 1979; Shepard 1992) and carcinogenicity (IARC 1981). As shown below, similar effects have been observed in animals and humans at roughly equivalent doses.

Studies of the mechanism of action of cyclophosphamide have demonstrated that the compound must be metabolized (activated) before it can exert its chemotherapeutic effects. It is first oxidized by the P450 system to form 4-hydroxycyclophosphamide, which is in a steady state with aldophosphamide, its acyclic tautomer (Chabner *et al.*

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Table 1. Occupational exposure limits for noncarcinogenic pharmaceutical compounds.

Compound	Data Source	Daily Dose (mg/kg)	Critical Endpoint	UF	OEL <sup>1</sup> (mg/m <sup>3</sup> )
Acetylsalicylic acid	Human	0.6	Clinical LOEL for anticoagulation therapy and NOEL for closure of ductus arteriosus	30 UF <sub>H</sub> UF <sub>L</sub>	0.1
	Rat	10	LOEL for closure of ductus arteriosus parturition delay and increased fetal bleeding	180 UF <sub>H</sub> UF <sub>L</sub> UFA	0.3
Clofibrate	Human	5	LOEL for decrease in serum triglycerides	30 UF <sub>H</sub> UF <sub>L</sub>	0.8
	Rat	90	LOAEL for induction of hepatic peroxisomal proliferation	180 UF <sub>H</sub> UF <sub>L</sub> UFA	2.5
Indomethacin	Human	0.75	LOAEL for inhibition of prostaglandin synthesis	30 UF <sub>H</sub> UF <sub>L</sub>	0.1
	Lamb	0.5	LOAEL for fetal death	60 UF <sub>H</sub> UF <sub>L</sub> UFA	0.04

<sup>1</sup>OELs established as 8-hour time weighted averages

1996). Further metabolism produces both inactive metabolites via enzymatic conversion and toxic metabolites by nonenzymatic mechanisms. The latter generate phosphoramidate mustard, a strong alkylating agent, and acrolein, a highly irritating compound that produces necrosis of the bladder epithelium if sulfhydryl compounds (*e.g.*, MESNA) are not co-administered (Chabner *et al.* 1996). *In vitro* and *in vivo* genotoxicity studies have confirmed the potential for cyclophosphamide to damage DNA (Bryant *et al.* 1989; Moore *et al.* 1995). Establishment of an occupational exposure limit for cyclophosphamide must obviously take the genotoxic effects of the drug into account; however, it is not clear, *a priori*, whether animal or human data (or both) should be used to derive a limit.

### Animal Data

Cyclophosphamide has a moderate order of acute oral and intravenous toxicity with LD50s in rats of 180 and 160 mg/kg, respectively (IARC 1981). The predominant finding in repeat-dose studies in mice, rats and dogs was hematological toxicity (*e.g.*, leukopenia and thrombocytopenia). Other target organs identified were the lungs, gut, pancreas and liver. As with all cytotoxic drugs, rapidly dividing tissues are the most susceptible. Cyclophosphamide is teratogenic in mice, rats, rabbits and rhesus monkeys at dosages as low as 2.5 mg/kg/day (McClure *et al.* 1979). Embryotoxic effects have also been reported in several species (Shepard 1992). Damage was produced to DNA in spermatozoa from adult male rats exposed to 6.1 mg/kg/day for 1 or 6 weeks (Qui *et al.* 1995).

Cyclophosphamide has also been shown to be carcinogenic in mice and rats following oral, subcutaneous, intramuscular and intraperitoneal administration (IARC 1981). In addition to local tumors produced at the site of injection with parenteral dosing, a variety of malignant tumors have been observed, including those observed as secondary malignancies in cancer patients (*e.g.*, leukemias and bladder tumors). Schmahl and Habs (1979) reported a significant increase in tumors of the urinary bladder and the lymphoid and hematopoietic tissues in rats exposed to cyclophosphamide in drinking water in a lifetime study at dosages of 0.31 to 2.5 mg/kg/day. The tumor incidence data from this study are reproduced in Table 2. Sessink *et al.* (1995) used this study to estimate the cancer potency of cyclophosphamide to compare to similar estimates based on data from cancer patients with secondary malignancies (see below).

### Human Data

Cyclophosphamide is used alone or in combination with other antineoplastic agents to treat Hodgkin's disease, malignant lymphomas, multiple myeloma, leukemias, mycosis fungoides, neuroblastoma, ovarian neoplasms, retinoblastoma and breast cancer (AHFS 2001). Various dosing regimes are used ranging from induction of therapy with 40 to 50 mg/kg IV for 2 to 5 days to daily oral initial and maintenance doses of 1 to 5 mg/kg/day. Dosages are adjusted based on total white blood cell counts to limit the degree of bone marrow suppression, a significant adverse effect associated with chemotherapy.

Unlike other pharmaceuticals with an adequate therapeutic index (*i.e.*, when the dosage associated with toxicity is much higher than the therapeutic dose), serious

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Table 2. Establishment of an OEL for cyclophosphamide using cancer as the critical endpoint.

Data Source	Daily Dose (mg/kg/day)	Leukemia Incidence	Cancer Risk at 1 $\mu\text{g/day}$ *
Rat <sup>1</sup>	0.31-2.5	4-7%	$3.3 \times 10^{-4}$
Human <sup>2</sup>	1.0-5.0	5.4%	$0.6 \times 10^{-4}$

\*Prop 65 NSRL = 1  $\mu\text{g/day}$  ( $1 \times 10^{-5}$  excess cancer risk) using bladder tumor data from Schmahl and Habs (1979). Risk estimates derived from Sessink *et al.* (1995).

<sup>1</sup>Schmahl and Habs (1979)

<sup>2</sup>Green *et al.* (1986)



toxic effects are an expected consequence of cancer chemotherapy with cyclophosphamide. As mentioned above, the most prominent adverse effects reflecting bone marrow suppression include leukopenia, thrombocytopenia, hypofibrinogenemia, and anemia (AHFS 2001). Alopecia, nausea and vomiting also occur frequently. Pulmonary fibrosis and cardiotoxicity are only reported in patients receiving high doses of cyclophosphamide. Birth defects have been reported in the offspring of cancer patients treated during pregnancy and the abnormalities observed (*e.g.*, ectrodactylia) are similar to those reported in animals. Gonadal suppression and sterility may occur in both male and female patients (AHFS 2001).

Some patients receiving cyclophosphamide, either alone or in combination with other chemotherapeutic agents, have developed secondary malignancies several years after completion of initial cancer therapy (IARC 1981). These are generally malignancies of the urinary bladder (especially in patients that developed hemorrhagic cystitis due to the irritant action of the metabolite acrolein), and myeloproliferative and lymphoproliferative malignancies. Secondary malignancies typically develop within 2 to 3 years after cessation of initial chemotherapy, although the latency of some tumors may be much longer.

#### Derivation of an OEL for Cyclophosphamide

The critical endpoint for deriving a health-based limit for cyclophosphamide is cancer. As discussed above, extensive *in vitro* studies confirm that cyclophosphamide, once biotransformed to its active form, produces genotoxic effects via alkylation and cross-linking of DNA strands and associated proteins. Cyclophosphamide is therefore considered a direct-acting genotoxic material and its mode of action supports a linear extrapolation approach for estimating risk.

The State of California (1993), under Proposition 65 legislation, used the rat bladder tumor incidence data from Schmal and Habs (1979) to calculate a cancer slope factor (CSF) of  $0.57 \text{ (mg/kg/day)}^{-1}$  for cyclophosphamide. The corresponding no-significant-risk level (NSRL) is  $1 \text{ }\mu\text{g/day}$  ( $1 \times 10^{-5}$  excess lifetime cancer risk), the only current regulatory value available for cyclophosphamide. The drug is also regulated in the state as a reproductive hazard. No adverse effects on organ systems or the developing fetus are expected at this level of exposure (*i.e.*, protecting against cancer should protect against all other adverse effects).

Sessink *et al.* (1995) calculated a cancer slope factor using the same study (Schmal and Habs 1979) but rather chose the leukemia incidence data as the basis of their CSF. They then derived a second slope factor from an evaluation of 3363 1-year survivors of ovarian cancer that received cumulative doses ranging from 7.6 to over 30 grams; approximately 5% developed secondary malignancies (Green *et al.* 1986). An estimate of cancer potency was derived from the animal data by linear extrapolation to zero from the lowest dose that produced a significant increase in tumors. Cancer risks for cyclophosphamide of  $2.3$  to  $2.9 \times 10^{-4} \text{ (mg/kg)}^{-1}$  were first calculated by dividing the tumor incidence by the total cumulative doses received by the animals. Cancer risks of 0.21 to 0.24% per gram of cyclophosphamide, or  $1.5 \times 10^{-4} \text{ (mg/kg)}^{-1}$ , were derived in a similar fashion from tumor incidence data from cancer patients.

Based on the analysis of Sessink *et al.* (1995), exposure to the NSRL of  $1 \text{ }\mu\text{g/day}$  would be associated with an excess cancer risk of  $3.3 \times 10^{-4}$  based on the animal data

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and  $0.6 \times 10^{-4}$  based on the human data. The sixfold difference in these estimates may seem significant; however, they should be put into perspective relative to the multiple orders of magnitude extrapolation from the doses associated with the observed tumors. Use of the human data to estimate cancer risk is preferred because they are most relevant to the target population being protected (*i.e.*, workers) and are of sufficient quality to support derivation of a quantitative health-based exposure limit. Dividing the  $1 \mu\text{g}/\text{day}$  NSRL value recommended under Prop 65 by  $10 \text{ m}^3$  yields an OEL of  $0.1 \mu\text{g}/\text{m}^3$ , which represents an acceptable level of cancer risk. It is noteworthy that, in this situation, an OEL could be derived solely from the human data. The animal data gave essentially similar risk estimates and corroborated the human data.

### INDOMETHACIN

Indomethacin is a member of a class of prescription drugs known as non-steroidal anti-inflammatory drugs (NSAIDs) that are used for their anti-inflammatory, anti-pyretic and analgesic properties. In particular, indomethacin has been found effective for treatment of moderate to severe rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis. In addition, indomethacin is used to treat tocolysis (premature labor) and polyhydramnios (excess amniotic fluid) in pregnant women (Lione and Scialli 1995). Finally, in premature infants, intravenous administration of indomethacin is the conventional pharmacological treatment used to promote closure of patent ductus arteriosus (PDA) (van Overmeire *et al.* 1995) as oral absorption in neonates is poor (~15 to 20%) (Bhat *et al.* 1980).

### Animal Data

The primary toxic effect of indomethacin in experimental animals is ulceration of the gastrointestinal tract. The doses of indomethacin tolerated by experimental animals, particularly the dog and rat, are lower than those tolerated in man. The oral  $\text{LD}_{50}$  (14-day observation period) of indomethacin in rats and mice is 12 and 50 mg/kg, respectively. The oral  $\text{LD}_{50}$  of indomethacin in rats using a 2-day observation period is 1110 mg/kg. Subacute and chronic toxicity studies of indomethacin revealed that the principal toxic effect, similar to other NSAIDs, is ulceration of the gastrointestinal tract.

Indomethacin was not genotoxic in a battery of *in vitro* (with or without metabolic activation) or *in vivo* tests. In oncogenicity tests in rats and mice, indomethacin produced no neoplastic or hyperplastic changes related to treatment at doses up to 1.5 mg/kg/day (Medical Economics Company 2001a).

In teratogenicity studies, indomethacin administered to mice and rats at a dose of 4.0 mg/kg/day during the last 3 days of gestation resulted in decreased maternal weight gain and some maternal and fetal deaths (Medical Economics Company 2001a). At this dose, live-born fetuses had an increased incidence of neuronal necrosis in the diencephalon. No increase in neuronal necrosis occurred at a dose of 2.0 mg/kg/day, or if administered postnatally at doses up to 4.0 mg/kg/day (Medical Economics Company 2001a). In addition, low maternal dosing (0.5 mg/kg) of pregnant ewes has been shown to be lethal to fetuses due to acute constriction of the fetal ductus arteriosus (Lione and Scialli 1995). The fetal blood concentra-

tions in the lamb were generally lower than the maternal ewe blood concentrations (0.1 mg/dl [1 µg/ml] vs. 0.12 to 0.77 mg/dl [1.2 to 7.7 µg/ml]). However, these blood concentrations are higher than those observed in clinical studies. In studies done by Verbesselt *et al.* (1983), humans given twice the dose given to pregnant ewes resulted in 3.5- to 18-fold lower plasma concentrations. This difference may explain much of the greater sensitivity of this species.

### Human Data

The recommended clinical oral dosage is one 25-mg or 50-mg capsule, two or three times daily (*i.e.*, 50 to 150 mg/day). The maximum daily dose is 150 to 200 mg/day, or 4 mg/kg/day, whichever is less (Medical Economics Company 2001a). Inhibition of prostaglandin synthesis is seen at doses as low as 37.5 mg/day (Rane *et al.* 1978). Orally administered indomethacin is virtually 100% bioavailable, with 90% of the dose absorbed within 4 hours. The most common symptoms associated with indomethacin use are gastrointestinal complaints, central nervous system complaints, and tinnitus (Medical Economics Company 2001a). Less common symptoms include gastrointestinal ulceration and bleeding and perforation. These side effects are associated with long-term use of other NSAIDs. Intravenous administration of indomethacin for treatment of patent ductus arteriosus in preterm infants has been shown to cause vascular irritation (thrombophlebitis) at an incidence of 1 to 3% (Medical Economics Company 2001b).

Like aspirin and most other NSAIDs, indomethacin inhibits platelet aggregation and may prolong bleeding time at therapeutic doses. However, unlike salicylates like aspirin, indomethacin is a rapidly reversible inhibitor of prostaglandin synthetase and recovery of platelet function may occur within 1 day after discontinuation of the medication (Medical Economics Company 2001a).

Indomethacin crosses the human placenta and maternal and fetal serum concentrations are similar (Moise *et al.* 1990). Use of NSAIDs in the third trimester of pregnancy is contraindicated because of a variety of adverse effects on the fetus (precipitated by the premature constriction or closure of the ductus arteriosus in fetuses in the 27th through 35th weeks of gestation). However, in cases of premature labor or polyhydramnios the high risk for the myriad of adverse outcomes, especially death, faced by preterm births is weighed against the benefit of *in utero* prophylaxis.

### Derivation of an OEL

As a result of the species sensitivity differences to indomethacin noted above, it is inappropriate to base a quantitative evaluation of indomethacin for human health on animal data. Animals are far more sensitive to, and far more likely to develop, gastrointestinal ulceration from both acute and chronic dosing. Within the human population, the fetus potentially represents the most sensitive subgroup to the effects of indomethacin and the maternal/fetal serum ratio is 0.97 (Moise *et al.* 1990). However, because extremely high plasma concentrations of indomethacin, consistent with doses at or above the maximum daily therapeutic dose, are necessary to trigger the untoward effects, fetal protection was not selected as the basis of the OEL. Instead, the critical endpoint for deriving an OEL is the subtherapeutic dose that causes inhibition of prostaglandin synthesis.

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For adults, an acceptable daily intake (ADI) of 1.2 mg/day was derived based on the inhibition of prostaglandin synthesis seen at the lowest pharmacologically effective dose of 37.5 mg/day (Rane *et al.* 1978) and adjusted downward 10-fold to account for interindividual variability ( $UF_H$ ) and 3-fold for the use of a LOEL ( $UF_L$ ). This results in an OEL of 0.1 mg/m<sup>3</sup>, a value, which provides an adequate margin of safety over clinical doses, used to treat pregnant women in the third trimester and thus would be protective of all individuals including fetuses.

### CLOFIBRATE

Clofibrate is an antihyperlipidemic agent, which reduces serum levels of triglyceride-rich, very low-density lipoproteins (VLDL) and, to a lesser extent, cholesterol and cholesterol-rich, low-density lipoproteins (LDL). It also lowers serum free fatty acids. It is rarely used today but was used effectively to reduce plasma concentration of triglycerides and cholesterol as an adjunct to dietary treatment. The exact mechanism by which clofibrate lowers serum concentrations of triglycerides and cholesterol is unknown but includes inhibition of hepatic triglyceride synthesis and increased secretion of cholesterol into bile, activation of lipoprotein lipase and suppression of free fatty acid release from adipose tissue (IARC 1983).

### Animal Data

In repeat-dose toxicity studies in animals, significant species-specific variability in response to clofibrate has been shown due to differences in the extent of peroxisomal proliferation. The hepatic effects of clofibrate treatment in a feeding study in male and female rats included peroxisome proliferation characterized by increased number of peroxisomes, peroxisomal enzymatic activity and hepatocellular hyperplasia (Tanaka *et al.* 1992). The lowest-observed adverse effect level (LOAEL) was 90 mg/kg/day. Other repeat-dose studies in rodents resulted in accumulation of lipofuscin pigment (Marsman *et al.* 1992) and increased oxidative DNA damage (Cattley and Glover 1993). *In vitro* studies in hepatocytes of rat and human origin have demonstrated that the induction of peroxisomal proliferation is a direct result of action of clofibrate on hepatocytes.

Clofibrate produced increased peroxisomal proliferation in fetal livers in mice at 400 mg/kg maternal body weight per day (Wilson *et al.* 1991), and also resulted in significant fetotoxicity (decreased birth weight, viability and litter size in rats) (LOAEL = 150 mg/kg/day) (Nyitray *et al.* 1980). Clofibrate was not teratogenic in rats (Diener and Hsu 1966). Reproduction studies in both dogs and monkeys using clofibrate dosages approximately 4-6 times the usual human dosage have been shown to arrest spermatogenesis (McEvoy 1995). It was not genotoxic in numerous *in vitro* and *in vivo* studies as summarized in IARC (1996). A slight increase in the level of 8-hydroxyguanosine was detected in liver DNA of rats fed clofibrate in the diet (Cattley and Glover 1993).

The carcinogenicity of clofibrate was tested in several studies in rats and mice following administration in the diet and in marmosets after gastric instillation. Several 18-month studies in which mice received clofibrate in the diet (150 to 5000 mg/kg/day) resulted in no differences in the induction of any tumor type (Tucker and Orton 1995). Similar studies in rats treated with dosages of 250 mg/kg/day and

higher resulted in significant increases in the incidence of hepatocellular carcinomas and pancreatic acinar carcinomas (Reddy and Qureshi 1979; Svoboda and Azarnoff 1979; Greaves *et al.* 1986). One study in marmosets treated orally with clofibrate at doses up to 263 mg/kg/day for 6.5 years resulted in no treatment-related tumors (Tucker and Orton 1995). A collective review of available data has resulted in the classification of clofibrate as an IARC-Group 3 carcinogen, not classifiable as to its carcinogenicity in humans, despite limited evidence of carcinogenicity in experimental animals (IARC 1996).

### Human Data

The recommended clinical dose of clofibrate is 1 to 2 grams daily in 2 to 4 divided doses. The lowest clinically active dose is 250 mg/day. It is rapidly and almost completely absorbed from the gastrointestinal tract. Maximum plasma concentrations occur at about 4 to 6 hours after oral administration. It is rapidly hydrolyzed to the acid by tissue and serum esterases. The majority (95 to 99%) of an orally administered dose is excreted in urine as free and conjugated clofibrinic acid. Clofibrinic acid is the therapeutically active metabolite of clofibrate. The majority of plasma drug is protein-bound in humans (>90%), somewhat greater than that seen in animals (75 to 87%). Clofibrinic acid has a mean elimination half-life of 18 to 22 hours in humans and 4.1 hours in animals. Clofibrate is contraindicated in patients with known hypersensitivity to the drug, in pregnant or nursing women, and in patients with hepatic or renal dysfunction and primary biliary cirrhosis. The most common adverse effects include nausea, headache, dizziness, fatigue, drowsiness and weakness (AHFS 2000). Several serious side effects have resulted after long-term use of clofibrate, including cholestasis, skeletal myopathy, and arrhythmias. Clofibrate use has also been associated with impotence and decreased libido in men.

Because of the hepatic changes noted in rodents, the effects of clofibrate and clofibrinic acid on human hepatocytes have been studied following *in vivo* and *in vitro* exposures. No statistically significant increase in the number, volume or density of peroxisomes in hepatocytes was observed in several groups of patients administered doses of clofibrate of 0.5 g/day and higher for up to 7 years (Hanefeld *et al.* 1980, 1983). *In vitro* assays in human primary hepatocytes and hepatoma cell lines also did not demonstrate induction of peroxisomal proliferation.

The human carcinogenic potential of clofibrate became a concern as a result of the 1978 World Health Organization (WHO) randomized trial. This trial showed a nonsignificant excess of cancer deaths in treated individuals. Subsequently, the association between cancer and clofibrate treatment was investigated in several additional randomized trials, a small case-control study and a four-year follow-up of the WHO trial. In each of these studies no difference in age-standardized death rates from malignant neoplasms was observed when compared with placebo patients. A meta-analysis of several trials also found no excess cancer mortality due to clofibrate use (CPI 1978, 1980, 1984; IARC 1980; Canner *et al.* 1986; Carlson and Rosenhamer 1988).

### Derivation of an OEL for Clofibrate

The adverse effects and carcinogenicity of clofibrate appear to be rodent-specific. The available data indicate that it does not act as a direct DNA-damaging agent and

## Human Data in Occupational Exposure Limits

that its mechanism of tumor induction is indirect. Clofibrate induces peroxisome proliferation and increases hepatocellular proliferation in rats. Tumor response in rodents is secondary to peroxisome proliferation via the peroxisome proliferator activated receptor PPAR, a member of the nuclear steroid hormone receptor superfamily associated with peroxisome proliferation and liver cancer (Corton *et al.* 2000). Evidence of peroxisome proliferation has not been found in human trials and *in vitro* systems derived from humans. Low expressions of PPAR mRNA in human liver leads to a lack of response to rodent-peroxisome proliferation. These findings indicate that the increased liver tumor incidence in rodents after clofibrate treatment results from a mechanism that is not active in humans. Consideration of this critical endpoint in estimating a safe level of chronic exposure of humans to clofibrate therefore is not appropriate.

For comparison purposes, in calculating an ADI from animal studies, the induction of hepatic peroxisome proliferation in rats (LOAEL = 90 mg/kg/day) would have been the critical endpoint used. The uncertainty factors (UFs) that need to be applied to the sensitive endpoint in estimating an ADI are 10 to account for human interindividual variability ( $UF_H$ ), 6 to account for animal to human extrapolation ( $UF_A$ ) and 3 to account for LOAEL to NOAEL ( $UF_L$ ) extrapolation. The resulting composite uncertainty factor ( $UF_C$ ) is 180. Assuming a body weight of 50 kg for a healthy adult and applying the  $UF_C$  to the LOAEL, an ADI of 25 mg/day can be estimated. An occupational exposure limit (OEL) of 2.5 mg/m<sup>3</sup> would be calculated from the estimated ADI by assuming that 10 m<sup>3</sup> of air are inhaled per each 8-hour working day (Table 1).

Using human data, an OEL of 0.8 mg/m<sup>3</sup> was calculated utilizing the lowest clinically active dose reported in patients (250 mg/day). In this instance, the UFs that need to be applied to the lowest clinically active dose are a  $UF_H$  equal to 10 and a  $UF_L$  equal to 3, resulting in a  $UF_C$  of 30. The resulting ADI and OEL are 8 mg/day and 0.8 mg/m<sup>3</sup>, respectively (Table 1). In the case of clofibrate the use of human data precludes the need for animal to human extrapolation and minimizes the potential for use of an inappropriate animal model to estimate human risk.

## DISCUSSION

The establishment of occupational exposure limits for four pharmaceutical compounds — acetylsalicylic acid, cyclophosphamide, indomethacin and clofibric acid afforded the opportunity to explore the use of animal and human data in the limit setting process. Extensive published animal and human (clinical, epidemiological, and anecdotal) data were available for all four compounds. As with all good risk assessments, the entire available data set (both animal and human) was used to establish the OEL; however, the human data set was used to identify the critical endpoint and critical dose in each case. The rationale for selection of human data over animal data differed for each compound and was largely based on the professional judgment of the risk assessor.

By ignoring the human data, we also derived OELs for each compound using the available animal data. For two of the compounds, acetylsalicylic acid and clofibrate, use of the animal data would result in a higher OEL than that derived from human data. In the case of clofibrate differences in critical endpoint and use of uncertainty

factors accounted for the nearly 10-fold difference in the OELs. The human and animal-based OELs for ASA did not differ greatly. The selection of doses, however, in the animal studies played an important role in the derivation of no- or low-effect levels, as a large percentage of the animal studies employed doses well above the therapeutic range.

Use of animal data for indomethacin and cyclophosphamide would lead to the same or a higher OEL. The OEL for cyclophosphamide was based on the Prop 65 NSRL that is associated with a  $1 \times 10^{-5}$  excess cancer risk. Slightly different risk estimates were derived from the same chronic bioassay due to differences in selection of tumor type. Overall, the cancer risks calculated from the human data and the animal data were similar, one data set corroborated the other.

Indomethacin provides an interesting example in the importance of considering the full data set before developing risk estimates. In this case using reproductive toxicity data in the most sensitive animal species results in a lower exposure limit. The data indicate, however, that the increased sensitivity of animal models make them poor surrogates for estimating human risk.

It is a fundamental assumption within the pharmaceutical industry that humans are most often the appropriate species (within obvious ethical, and scientific and statistical limitations) on which to base risk assessments for protection of workers potentially exposed to pharmaceutical agents. Pharmaceutical compounds require clinical testing (pursuant to FDA-approved protocols) in humans by age, sex, and general health during Phases II and III, as a precondition for FDA approval. FDA requires demonstration of both safety and efficacy of different dosages in humans. In addition, FDA typically requires Phase IV postmarketing epidemiologic surveillance of adverse health effects for pharmaceuticals. Accordingly, a weight-of-evidence analysis that combines human, animal, and ancillary data should give significant deference to the clinical epidemiologic findings. While the criteria for assessing the adequacy of animal and epidemiologic studies are well recognized, no single factor is conclusive. OELs are often based on the collective professional judgment of a team of scientists from a variety of scientific disciplines. Nonetheless, some suggested considerations when evaluating the primacy of human vs. animal data include: (1) the relevance of animal toxicological findings to human health, especially suspected species-specific effects, (2) known differences in pharmacokinetics and pharmacodynamics, (3) the ability of clinical epidemiologic methods to detect specific adverse health endpoints (based on protocol measurements and duration of follow-up), and (4) the severity of the critical effect.

In summary, animal models and human studies are critical to the identification of potential hazards to human health. Properly conducted risk assessments must consider all data in order to be health protective. Risk assessors must be wary of overly prescriptive regulatory requirements or guidance that establish precedence for one form of data over another that are scientifically inappropriate (Schardein and Scialli 1999).

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